Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Proton pump inhibitors do not increase the risk of acute rejection

G.A.J. van Boekel*, C.H.H. Kerkhofs, F. van de Logt, L.B. Hilbrands

Department of Nephrology, Radboud University Medical Centre, Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)24-3614761; fax: +31 (0)24-3540022, e-mail: Gerben.vanBoekel@radboudumc.nl

ABSTRACT

Background: Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid (MPA). Proton pump inhibitors impair exposure to MPA due to incomplete conversion from MMF. Lower exposure to MPA could result in an increased risk of acute rejection. We investigated whether MMF-treated renal transplant patients who concomitantly used pantoprazole as ulcer prophylaxis had a higher risk of acute rejection within the first three months after transplantation than those who used ranitidine.

Methods: We performed a retrospective study in adult patients who underwent kidney transplantation between January 2007 and December 2011. Their immunosuppressive therapy consisted of steroids, tacrolimus and MMF and they used either pantoprazole or ranitidine as ulcer prophylaxis.

Results: 202 patients were included: 125 using pantoprazole and 77 using ranitidine. There was no difference in the number of patients with biopsy-proven acute rejection (BPAR): 13 (10.4%) in the pantoprazole group versus 7 (9.1%) in the ranitidine group (NS). Also after correction for inequalities between the two groups, there was no significant relationship between the risk of BPAR and the type of anti-ulcer agent.

Conclusion: There was no evidence for an increased incidence of BPAR in renal transplant patients who use pantoprazole in combination with MMF.

KEYWORDS

Acute rejection, kidney transplantation, mycophenolate mofetil, proton pump inhibitor

INTRODUCTION

Mycophenolate mofetil (MMF) is a commonly used immunosuppressive drug after solid organ transplantation and in autoimmune disease. After intake, MMF is rapidly absorbed and hydrolysed to its active metabolite, mycophenolic acid (MPA). MPA reversibly inhibits inosine monophosphate dehydrogenase, which is a key enzyme involved in the *de novo* purine synthesis in activated lymphocytes. Adequate exposure to MPA is associated with a decreased rate of acute rejection in kidney transplant patients.[1-4]

Proton pump inhibitors (PPI) are frequently prescribed post transplantation as prophylaxis for peptic ulcer disease, which is common and can cause significant morbidity and mortality.[5] During the last years, a series of studies have reported that PPI therapy decreases MPA exposure in kidney transplant patients, heart transplant patients, patients with autoimmune disease, and healthy volunteers.[6-10] Studies showed that concomitant use of pantoprazole 40 mg resulted in 34-37% lower exposure to MPA.[10,11] PPIs can raise the gastric pH level above 4, which results in a decreased de-esterification of MMF,[12] and thereby a reduction of the MPA plasma concentration. In our centre, peptic ulcer prophylaxis in recipients of a kidney transplant usually consists of either the PPI pantoprazole or the histamine 2 (H_2) receptor antagonist ranitidine. During the first day after administration, H_2 receptor antagonists usually elevate the gastric pH to a similar degree, or even more, than PPIs.[13,14] However, due to tolerance induction, the effect of H_2 receptor antagonists on gastric pH rapidly wanes during subsequent days, while the effect of PPIs strengthens. Thus, it can be expected that the effect of continuous use of H_2 receptor antagonists on MPA levels is considerably smaller than of PPIs. Currently, it is unknown whether the lower MPA exposure in patients treated with PPI has any clinical implications.

The present study therefore aimed to investigate whether MMF-treated renal transplant patients who concomitantly used pantoprazole had a higher risk of acute rejection within the first three months after transplantation than those who used ranitidine.

METHODS

Study design

We performed a retrospective cohort study to investigate whether MMF-treated kidney transplant patients, who concomitantly used pantoprazole (n=125), had an increased rate of acute rejection within the first three months after renal transplantation, compared with those who used ranitidine (n=77). The data were derived from medical records and a local database with transplant outcome data. According to Dutch law, Institutional Review Board approval was not required.

The primary outcome was the occurrence of biopsy-proven acute rejection (BPAR) within the first three months after transplantation. Histological examination and classification were done according to the Banff criteria.[15] A clinical diagnosis of presumed acute rejection was made when serum creatinine levels increased without another explanation and a biopsy was not performed. The secondary outcomes were the incidence of acute rejection (BPAR and presumed acute rejection) within three months after transplantation, BPAR and acute rejection within six months after transplantation, serum creatinine level, estimated glomerular filtration rate (eGFR) calculated by using the MDRD formula and proteinuria at three months after transplantation.

Patients

We included all adult patients who underwent renal transplantation in our centre between January 2007 and December 2011 and used a standard immunosuppressive therapy consisting of tacrolimus, prednisone and MMF with either ranitidine or pantoprazole, as ulcer prophylaxis. The choice between ranitidine and pantoprazole was made by the treating physician and usually depended on pre-existing use of either drug and personal preference of the treating physician. Exclusion criteria were: graft loss or death within the first three months after transplantation, treatment with drugs known to have a pharmacokinetic interaction with MMF (e.g. phosphate binders, rifampicin or cholestyramine), intravenous administration of MMF, combined use of ranitidine and pantoprazole, and switch between both drugs. Patients with a history of bowel surgery were also excluded.

A number of the patients (n=54) received induction therapy which consisted of basiliximab (n=6), daclizumab (n=1), or rituximab (n=47). Rituximab was given within the framework of a blinded, prospective, placebo-controlled trial (clinicaltrials.gov; NCT00565331). Patients were treated with prednisone 100 mg per day during the first three days after surgery and subsequently with prednisone 20-25 mg/day, which was gradually tapered to 0.1 mg/kg/day. On the first day after renal transplantation, tacrolimus was started in a dose of 0.2 mg/kg/day to target the trough level between 15-20 μg/l. During the first three months after transplantation, the dose of tacrolimus was gradually tapered to aim for a target range between 5-10 μg/l. The initial dose of MMF was 1000 mg twice daily and after two weeks this was decreased to 750 mg twice daily, except in patients who weighed more than 90 kg. If patients suffered from leucopoenia or gastrointestinal symptoms, the dose of MMF was reduced.

Acute rejections were initially treated with intravenous methylprednisolone 750-1000 mg for three consecutive days. If this treatment failed, patients received anti-thymocyte globulin (ATG, Thymoglobulin®), muromonab (Orthoclone OKT3®), or alemtuzumab (Campath®).

All patients started with either pantoprazole 40 mg/day (some patients accidentally started with pantoprazole 20 mg) or ranitidine 150 mg/day. These doses could be increased if patients had gastrointestinal complaints. Unless there were still symptoms, the ulcer prophylaxis was stopped after three months. All patients used co-trimoxazole as *Pneumocystis jirovecii* prophylaxis and valganciclovir was prescribed as prophylaxis if the renal transplant recipient was seronegative for cytomegalovirus while the donor was seropositive.

Statistical analysis

A threefold increase in the incidence of acute rejection might occur if patients have a 35% lower exposure to MPA in consequence of the combined use of pantoprazole and MMF in the early period after transplantation.[3,10,11] We expected a rejection rate of 15% in ranitidine-treated patients and made a conservative estimate of the rejection rate of 30% in the pantoprazole-treated patients. Based on these rejection rates, a power of 0.8 and a type I error probability of 0.05, a sample size of 120 patients was required.

Normally distributed data are presented as mean with standard deviation (SD). Before analysis, data with a skewed distribution such as cold ischaemia time, panel reactive antibodies (PRA) and proteinuria were logarithmically transformed. We analysed our data with χ^2 test and unpaired T-test where appropriate. A multiple logistic regression analysis was carried out to evaluate whether variables, which were not equally distributed over both groups, affected the risk of BPAR. All statistical analyses were performed by using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the 202 patients who met the inclusion and exclusion criteria are summarised in *table 1*. The number of patients who received rituximab induction

Table 1. *Patient characteristics*

	Pantoprazole (n=125)	Ranitidine (n=77)	Significance p-value
Male (%)	61.6	66.2	NS
Age (years)	47.7 (12.8)	46.7 (13.3)	NS
Caucasian (%)	98.4	98.7	NS
Weight (kg)	74.3 (13.5)	75.4 (15.2)	NS
Length (cm)	173.9 (9.7)	175.1 (10.5)	NS
Living donor (%)	66.4	77.9	NS
PRA (%)	7.4 (1.2)	7.1 (1.3)	NS
Retransplantation (%)	15.2	7.8	NS
Cold ischaemia time in deceased donors (h)	18.05 (5.43)	15.17 (5.16)	NS
HLA mismatches on A, B and DR	3.2 (1.5)	3.2 (1.6)	NS
Donor age (years)	51.5 (10.8)	51.7 (11.3)	NS
CMV status (%)			
D+/R+	23.2	26.0	NS
D-/R+	18.4	23.4	NS
D+/R-	27.2	22.1	NS
D-/R-	30.4	27.3	NS
Induction therapy (%)			
Rituximab	17.6	32.5	<0.05
Basiliximab	3.2	2.6	NS
Daclizumab	0.8	0.0	NS
Delayed graft function (%)	2.4	3.9	NS
Cumulative dose of MMF in 3 months (g)	142.8 (18.0)	144.3 (18.1)	NS
Daily dose of prednisone at 3 months (mg)	10.1 (4.0)	10.8 (3.8)	NS
Daily dose of tacrolimus at 3 months (mg)	7.5 (4.2)	7.3 (4.0)	NS

Data are shown as mean (standard deviation) or percentage. CMV = cytomegalovirus; D = donor; HLA = human leucocyte antigen; MMF = mycophenolate mofetil, NS = not significant; PRA = panel reactive antigens; R = recipient; - = seronegative + = seropositive.

therapy differed significantly between the two groups. Small inequalities were present regarding cold ischaemia time, retransplantations, donor type, and cumulative dose of MMF. The daily dose of pantoprazole varied between 20-80 mg and the mean cumulative dose in three months was 3.9 g (standard deviation 1.0). The ranitidine dose varied between 150-300 mg per day, with a mean cumulative dose in three months of 14.4 g (2.4).

The percentage of patients with BPAR within three months after transplantation did not differ significantly between the two groups: 10.4% (n=13) in patients who used pantoprazole and 9.1% (n=7) in patients who used ranitidine. Thus, the difference in percentage of BPAR between the two groups is 1.3% (95% confidence interval -6.9% - 9.5%). There was also not a significant difference in the percentage of patients who had either BPAR or presumed acute rejection within three months after transplantation (20.0% (n=25) versus 19.5% (n=15)). In addition, the percentage of patients with BPAR or presumed acute rejection within six months after transplantation did not differ significantly between the two groups (*table 2*). The cumulative dose of MMF in patients with BPAR was 133.1 gram (14.3) and in patients without BPAR, it was 144.5 gram (18.1) (p<0.01). Creatinine level, eGFR, and level of proteinuria at three months after transplantation did not differ significantly between the two groups (*table 3*). Graft and patient survival was 100% in both groups at six months after transplantation.

Multiple logistic regression analysis was performed with the following covariates: race, age of the recipient, rituximab induction therapy, retransplantation, donor type, cold ischaemia time, PRA, human leukocyte antigen (HLA) mismatches, delayed graft function, cumulative dose of MMF, and type of anti-ulcer agent. Using BPAR within three months as dependent variable, the only statistically significant covariates were cumulative dose of MMF (p<0.01), race (p<0.05) and retransplantation (p<0.05). The type of anti-ulcer agent had no effect on the risk of BPAR.

Since the dose of pantoprazole varied between patients, we evaluated the correlation between the cumulative dose of pantoprazole within the first three months after transplantation and the incidence of BPAR. There was no significant association between exposure to pantoprazole and risk of acute rejection.

Table 2. *Percentage of patients with acute rejections within 3 or 6 months after transplantation*

	Pantoprazole (n=125)	Ranitidine (n=77)	Significance p-value
BPAR within 3 months	10.4%	9.1%	NS
BPAR or presumed acute rejection within 3 months	20.0%	19.5%	NS
BPAR within 6 months	12.0%	10.4%	NS
BPAR or presumed acute rejection within 6 months	21.6%	20.8%	NS

BPAR = biopsy-proven acute rejection; NS = not significant.

Table 3. *Creatinine, eGFR and proteinuria at 3 months after transplantation in both groups*

	Pantoprazole (n=125)	Ranitidine (n=77)	Significance p-value
Creatinine (mg/dl)	1.5 (0.4)	1.5 (0.4)	NS
eGFR (ml/min/1.73m²)	49.5 (12.3)	50.7 (12.5)	NS
Proteinuria (g/10 mmol creatinine)	0.25 (2.68)	0.15 (0.25)	NS

eGFR = estimated glomerular filtration rate; NS = not significant

DISCUSSION

In this retrospective study we did not observe an increased risk of acute rejection within the first three months after renal transplantation in patients using pantoprazole in combination with MMF. Accordingly, there was no relationship between the dose of pantoprazole and the risk of acute rejection.

After oral administration, MMF is rapidly absorbed and undergoes extensive presystemic de-esterification by esterases to MPA. The MPA peak concentration is reached within 1-2 hours. Several investigators showed that PPI co-medication leads to a 34-37% reduction of MPA exposure.[10,11] The impairment of MPA exposure following co-administration of MMF and PPI has been demonstrated for pantoprazole, lansoprazole, and omeprazole.[6-11] The most commonly prescribed PPI in our centre is pantoprazole. Pantoprazole 40 mg produces a strong and consistent gastric acid suppression.[16] Morning or evening intake of pantoprazole is irrelevant because intra-gastric pH elevation under PPI treatment is a permanent effect due to the irreversible inhibition of the gastric proton pump.[16] A higher dose of pantoprazole leads to a higher gastric pH and to a lower solubility of MMF since it was approximately 4 mg/l in a buffer with a pH of 4, but only 0.24 mg/l at a pH of 5.2 and only 0.04 mg/l at a pH of 7.[17] A secondary peak in the concentration-time profile of MPA occurs after 6-12 hours because of enterohepatic circulation. This secondary peak in the concentration-time curve is not reduced by use of PPI since no significant changes in MPA plasma concentrations between 2-12 hours after the intake were found in patients using a PPI.[10] Previous studies have shown that a lower exposure to MPA increases the incidence of acute rejection after renal transplantation.[1-4] On the basis of these data, we hypothesised that the use of PPI in MMF-treated renal transplant patients might result in an increased incidence of acute rejection. As far as we know our study is the first that specifically addresses this issue.

The risk of acute rejection did not differ between pantoprazole- and ranitidine-treated patients, despite a slightly lower total cumulative dose of MMF in the pantoprazole group. Based on an approximately 35% lower exposure to MPA in patients who used the combination of pantoprazole and MMF in the early period after transplantation, a threefold increase in the incidence of acute rejection might occur.[3,10,11] The rejection incidence of 10.4% in the pantoprazole group as well as the relatively narrow 95% confidence interval for the difference with the ranitidine group (-6.9% – 9.5%) make such an increase in rejection incidence highly unlikely.

While most studies indicate that the combined use of PPI and MMF leads to a lower MPA exposure, Kiberd *et al.* recently found no significant impact of PPI use on total MPA exposure at day 5 after transplantation, although blood levels at two and 12 hours postdose were significantly reduced.[18] Because we did not measure MPA levels and gastric pH, we were not able to show a pharmacokinetic interaction between MMF and PPI in our patients. However, the magnitude of such an effect was apparently not large enough to have clinical consequences. Moreover, our study is limited by its retrospective design, which impedes correction for unknown confounders. Furthermore, it should be noted that patients who used cyclosporine were not included in this study. Because cyclosporine has an inhibitory effect on the enterohepatic circulation of MPA, cyclosporine-treated patients might be more prone to underexposure to MPA when MMF is combined with a PPI. Similarly, potential underexposure to MPA might be more problematic in African American patients who were nearly absent in our study population.[19] Finally, since we only investigated the effect of concomitant use of pantoprazole and MMF during the first three months after transplantation, we cannot rule out that longstanding concomitant use does increase the incidence of rejection. However, David-Neto *et al.* recently showed that the effect of simultaneous use of PPI and MMF on MPA exposure was particularly present in the first week post-transplantation.[20] Moreover, an increased rejection incidence has especially been associated with inadequate exposure to MPA in the early period after transplantation.[2,4]

In conclusion, we found no evidence for a higher incidence of acute rejection in patients using pantoprazole in combination with MMF. This was supported by the absence of a significant relationship between the dose of pantoprazole and incidence of acute rejection.

DISCLOSURE

No funding sources for this study. LH received grants for clinical studies from Astellas, Roche and Novartis. The other authors have no other relevant financial relationships to disclose.

REFERENCES

1. van Gelder T, Hilbrands LB, Vanrenterghem Y, et al. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. Transplantation. 1999;68:261-6.
2. Kiberd BA, Lawen J, Fraser AD, Keough-Ryan T, Belitsky P. Early adequate mycophenolic acid exposure is associated with less rejection in kidney transplantation. Am J Transplant. 2004;4:1079-83.
3. Le Meur Y, Buchler M, Thierry A, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7:2496-503.

4. van Gelder T, Silva HT, de Fijter JW, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. Transplantation. 2008;86:1043-51.
5. Logan AJ, Morris-Stiff GJ, Bowrey DJ, Jurewicz WA. Upper gastrointestinal complications after renal transplantation: a 3-yr sequential study. Clin Transplant. 2002;16:163-7.
6. Miura M, Satoh S, Inoue K, et al. Influence of lansoprazole and rabeprazole on mycophenolic acid pharmacokinetics one year after renal transplantation. Therapeutic Drug Monit. 2008;30:46-51.
7. Kofler S, Deutsch MA, Bigdeli AK, et al. Proton pump inhibitor co-medication reduces mycophenolate acid drug exposure in heart transplant recipients. J Heart Lung Transplant. 2009;28:605-11.
8. Rupprecht K, Schmidt C, Raspe A, et al. Bioavailability of mycophenolate mofetil and enteric-coated mycophenolate sodium is differentially affected by pantoprazole in healthy volunteers. J Clin Pharmacol. 2009;49:1196-201.
9. Doesch AO, Mueller S, Konstandin M, et al. Proton pump inhibitor co-medication reduces active drug exposure in heart transplant recipients receiving mycophenolate mofetil. Transplant Proc. 2010;42:4243-6.
10. Schaier M, Scholl C, Scharpf D, et al. Proton pump inhibitors interfere with the immunosuppressive potency of mycophenolate mofetil. Rheumatology. 2010;49:2061-7.
11. Kofler S, Shvets N, Bigdeli AK, et al. Proton pump inhibitors reduce mycophenolate exposure in heart transplant recipients-a prospective case-controlled study. Am J Transplant. 2009;9:1650-6.
12. Kees MG, Steinke T, Moritz S, et al. Omeprazole impairs the absorption of mycophenolate mofetil but not of enteric-coated mycophenolate sodium in healthy volunteers. J Clin Pharmacol. 2012;52:1265-72.
13. Hurlimann S, Abbuhl B, Inauen W, Halter F. Comparison of acid inhibition by either oral high-dose ranitidine or omeprazole. Aliment Pharmacol Therapeut. 1994;8:193-201.
14. Netzer P, Gaia C, Sandoz M, et al. Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. Am J Gastroenterol. 1999;94:351-7.
15. Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: updates and future directions. Am J Transplant. 2008;8:753-60.
16. Tutuian R, Katz PO, Bochenek W, Castell DO. Dose-dependent control of intragastric pH by pantoprazole, 10, 20 or 40 mg, in healthy volunteers. Aliment Pharmacol Ther. 2002;16:829-36.
17. Lidgate D, Brandl M, Holper M, Abubakari A, Wu X. Influence of ferrous sulfate on the solubility, partition coefficient, and stability of mycophenolic acid and the ester mycophenolate mofetil. Drug Dev Ind Pharm. 2002;28:1275-83.
18. Kiberd BA, Wrobel M, Dandavino R, Keown P, Gourishankar S. The role of proton pump inhibitors on early mycophenolic acid exposure in kidney transplantation: evidence from the CLEAR study. Therapeutic Drug Monit. 2011;33:120-3.
19. van Gelder T, Tedesco Silva H, de Fijter JW, et al. Renal transplant patients at high risk of acute rejection benefit from adequate exposure to mycophenolic acid. Transplantation. 2010;89:595-9.
20. David-Neto E, Takaki KM, Agena F, et al. Diminished mycophenolic acid exposure caused by omeprazole may be clinically relevant in the first week posttransplantation. Therapeutic Drug Monit. 2012;34:331-6.