
# Prospective, 6 month, open label, conversion study from mycophenolate mofetil to mycophenolate acid evaluating the severity of gastro-intestinal symptoms and mycophenolic acid urinary metabolite as a surrogate marker of plasmatic area under the curve

Collette S[1], Lamarche C[1], Leblond F[2], Boucher A[1], Senécal L[1], Tran D[1], Pichette V[1,2].
1. Hôpital Maisonneuve-Rosemont, Université de Montréal, Montréal
2. Maisonneuve-Rosemont Research Center, Montréal

## Background

Treatment with mycophenolate mofetil (MMF) in the kidney transplant population often results in adverse gastro-intestinal (GI) events, which can lead to dose reductions that in turn can increase the risk of rejection. Studies have shown that mycophenolic acid (MPA) has a better GI side effect profile then mycophenolate mofetil (MMF) up to three months after initiation of treatment[1,2]. Measurement of 12 hours plasmatic MPA area under the curve (AUC) is the most accurate way to determine MPA exposure, but it is time and ressources consuming. MPA glucuronide (MPAG) is the most abundant metabolite of MPA and it is eliminated via the urine. The quantity of MPAG in the urine, if shown to correlate with plasma levels of MPA, could serve as a surrogate marker for plasmatic MPA AUC.

## Objectives

The first objective was to evaluate side effects of MPA on a six months basis. The second one was to evaluate correlation between urinary MPAG and plasmatic MPA.

## Methods

Open label single center study of 56 kidney transplant patients receiving MMF underwent an equimolar conversion to MPA. The study took place between September 2007 and December 2013. Patients filled the gastrointestinal symptom rating scale (GSRS) questionnaire at study entry, month 1,3 and 6. Thirteen of the 56 patients had 12 hours plasma MPA AUC and 12 hours urine content of MPAG measured by high performance liquid chromatography at month 1 and 3 after conversion.

## Results

Score for each dimension of the GSRS questionnaire decreases significantly as soon as one month after conversion and stays statistically significant up to 6 months when compared with baseline ($p<0.0001$) (Table 1). The diarrhea dimension goes from a mean of 4.7 points before conversion to a mean of 2.7 points at 6 months, which translates clinically from « moderately severe » diarrhea to a « mild discomfort » over time. Also, the total GSRS score drops almost 5 points over 6 months ($p<0.0001$). 85.2% of patients could tolerate initial or a higher dose of MPA.

Correlation between urinary amount of MPAG excreted in 12 hours and the 12 hours plasmatic MPA AUC was $r=0.82$ ($p=0.0011$) at month 1 (figure 1) and $r=0.87$ ($p=0.0002$) at month 3 (figure 2) and remained statistically significant with a correction for the glomerular filtration rate ($r=0.93$ ($p<0.0001$) at month 1 and $r=0.84$ ($p=0.0004$) at month 3). Kidney function and the cell blood counts were stable throughout the study.

**Table 1. Comparisons of the total GSRS score and the score of each dimension at month 1, 3 and 6 versus baseline**

| Variable | Comparison with baseline | Number of patients | Mean before | Mean after | Mean differences | p-value * |
|---|---|---|---|---|---|---|
| Diarrhea | Month 1 | 56 | 4.7 | 3.1 | -1.7 | < 0.0001 |
| | Month 3 | 55 | 4.6 | 2.7 | -1.9 | < 0.0001 |
| | Month 6 | 53 | 4.6 | 2.7 | -1.9 | < 0.0001 |
| Indigestion | Month 1 | 56 | 3.4 | 2.3 | -1.1 | < 0.0001 |
| | Month 3 | 55 | 3.3 | 2.3 | -1.0 | < 0.0001 |
| | Month 6 | 53 | 3.3 | 2.2 | -1.1 | < 0.0001 |
| Constipation syndrome | Month 1 | 56 | 2.2 | 1.9 | -0.4 | 0.0144 |
| | Month 3 | 55 | 2.3 | 1.8 | -0.5 | < 0.0001 |
| | Month 6 | 53 | 2.3 | 1.9 | -0.4 | 0.0120 |
| Abdominal pain | Month 1 | 56 | 2.6 | 2.0 | -0.6 | 0.0002 |
| | Month 3 | 55 | 2.6 | 1.9 | -0.6 | 0.0004 |
| | Month 6 | 53 | 2.5 | 1.8 | -0.8 | < 0.0001 |
| Reflux syndrome | Month 1 | 56 | 2.2 | 1.6 | -0.5 | 0.0097 |
| | Month 3 | 55 | 2.1 | 1.6 | -0.5 | 0.0052 |
| | Month 6 | 53 | 2.1 | 1.4 | -0.7 | < 0.0001 |
| GSRS total score | Month 1 | 56 | 15.0 | 10.9 | -4.2 | < 0.0001 |
| | Month 3 | 55 | 14.9 | 10.3 | -4.6 | < 0.0001 |
| | Month 6 | 53 | 14.8 | 9.9 | -4.9 | < 0.0001 |

*t-test for variables with normal distribution. Signed Rank test otherwise

**Figure 1. Correlation between plasmatic MPA $AUC_{0\text{-}12h}$ and urinary excretion of $MPAG_{0\text{-}12h}$ 1 month after conversion**

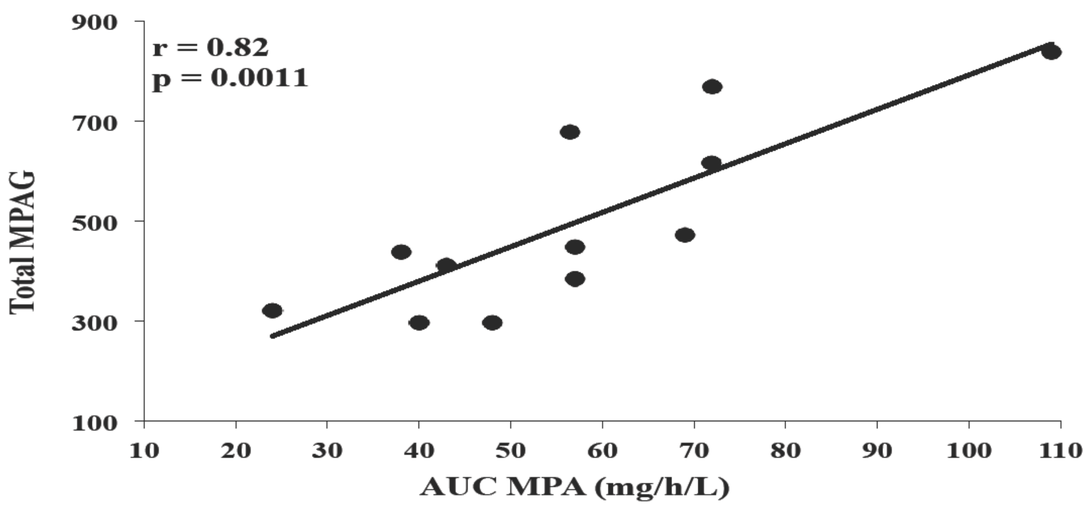
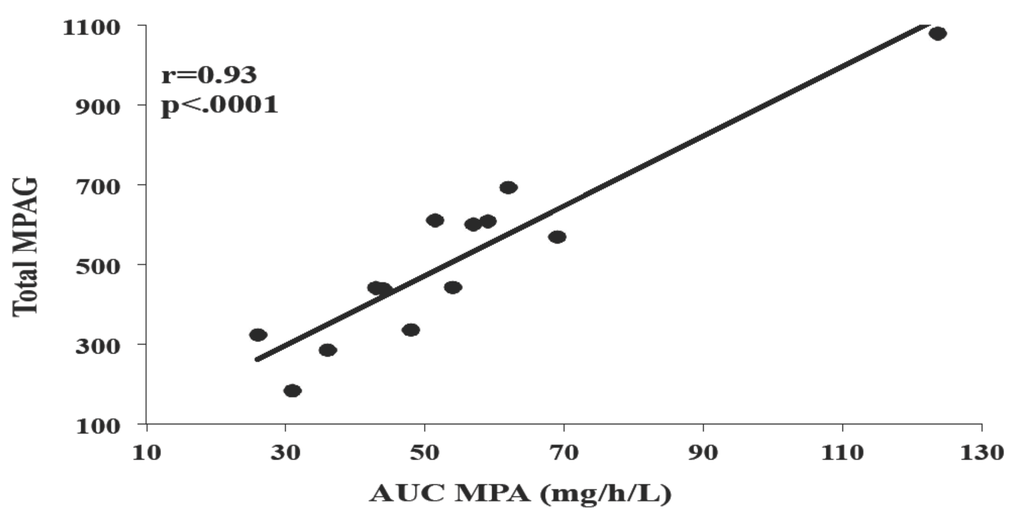



**Figure 2. Correlation between plasmatic MPA $AUC_{0\text{-}12h}$ and urinary excretion of $MPAG_{0\text{-}12h}$ 3 months after conversion**




## Conclusion

In our study, the conversion from MMF to MPA in stable kidney transplant recipients seems to be an effective and safe strategy to lower GI side effects, in more than 85% of patients. Furthermore, measuring the urinary MPAG excretion in a twelve-hour urine collection could be a practical and accurate surrogate marker for plasmatic MPA AUC.

## References

1. Chan L, Mulgaonkar S, Walker R, et al. Patient-reported gastrointestinal symptom burden and health-related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. Transplantation. 2006;81(9): 1290-7.
2. Bolin P, Tanriover B, Zibari GB, et al. Improvement in 3-month patient-reported gastrointestinal symptoms after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in renal transplant patients. Transplantation. 2007;84(11): 1443-51.

## Acknowledgement

This study was made possible through a research grant from Novartis Canada.