Mycophenolate Mofetil Therapeutic Drug Monitoring: Combined Multi-linear Regression and Bayesian Limited Sampling Area Under the Curve versus Standard Care

Ian C. Doyle PharmD  
*Pacific University School of Pharmacy*

Ahmed Zikri PharmD  
*Legacy Good Samaritan Hospital*

William M. Bennett MD  
*Legacy Good Samaritan Transplant Service*

Leslie M. Shaw PhD  
*University of Pennsylvania*

Michal J. Figurski PhD  
*University of Pennsylvania*

**Recommended Citation**

Doyle, Ian C. PharmD; Zikri, Ahmed PharmD; Bennett, William M. MD; Shaw, Leslie M. PhD; and Figurski, Michal J. PhD, "Mycophenolate Mofetil Therapeutic Drug Monitoring: Combined Multi-linear Regression and Bayesian Limited Sampling Area Under the Curve versus Standard Care" (2010). *Faculty Scholarship (PHRM)*. 33.  
[https://commons.pacificu.edu/phrmfac/33](https://commons.pacificu.edu/phrmfac/33)
Mycophenolate Mofetil Therapeutic Drug Monitoring: Combined Multi-linear Regression and Bayesian Limited Sampling Area Under the Curve versus Standard Care

Abstract
Therapeutic drug monitoring (TDM) of mycophenolate mofetil (MMF) has been investigated using multiple linear regression (MLR) and bayesian pharmacokinetics (BAY) independently. We hypothesize that performing TDM using simultaneous MLR and BAY for guidance in MMF dose selection will decrease acute rejection and risk of toxicity. Twenty-nine renal transplant (RT) patients were prospectively enrolled into a study of CellCept® (MMF, Roche), having their mycophenolic acid (MPA) levels monitored and dose adjusted to achieve target area under the curve (AUC) level of 45 mg.hr/L (range 40 – 50 mg.hr/L). This cohort is compared to 28 control patients prescribed standard of care, fixed dose MMF. MPA monitoring is associated with a non-significant decrease rate of acute rejection (AR) by 3 months. Increased rates of BK polyoma virus (BK) infection were observed by 3 months. The high frequency of MMF dose decreases on day 30 and 60 is consistent with literature that MPA AUC increases with time.

Disciplines
Pharmacy and Pharmaceutical Sciences

Rights
Terms of use for work posted in CommonKnowledge.

This poster is available at CommonKnowledge: https://commons.pacificu.edu/phrmfac/33
Mycophenolate Mofetil Therapeutic Drug Monitoring: Combined Multi-linear Regression and Bayesian Limited Sampling Area Under the Curve versus Standard Care

Ian C. Doyle1, Ahmed Zikri2, William M. Bennett3, Leslie M. Shaw4, Michal J. Figurski5

1Pacific University Oregon School of Pharmacy; 2Department of Pharmacy, Legacy Good Samaritan Hospital; 3Transplant Services, Legacy Good Samaritan Hospital; 4Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center

Abstract

Therapeutic drug monitoring (TDM) of mycophenolate mofetil (MMF) has been investigated using multiple linear regression (MLR) and Bayesian pharmacokinetics (BAY) independently. We hypothesize that performing TDM using simultaneous MLR and BAY for guidance in MMF dose selection will decrease acute rejection and risk of toxicity. Twenty-nine renal transplant (RT) patients were prospectively enrolled into a study of CellCept® (MMF, Roche), having their mycophenolic acid (MPA) levels monitored and dose adjusted to target area under the curve (AUC) level of 45 mg.h/L (range 40 – 50 mg.h/L). This cohort is compared to 28 control patients provided standard care, fixed dose MMF. MPA monitoring is associated with a non-significant decrease rate of acute rejection (AR) by 3 months. Increased rates of BK polyoma virus (BK) infection were observed by 3 months. The high frequency of MMF dose decreases on day 30 and 60 is consistent with literature that MPA AUC increases with time.

Methods

This study received approval from the Legacy Health System IRB. During the period of May 2009 to January 2010, 29 non-randomized RT patients were prospectively enrolled. MMF was initiated at the time of renal transplant. Patients concurrently received tapering doses of prednisone, and either tacrolimus (FK), cyclosporine (CSA), or rapamune, cyclosporine (CSA), or rapamune. Initial MMF dose: 1000 mg BID with FK, and 1500 mg BID with CSA. AUC samples were drawn on days 7, 30, and 60 post-transplantation. Limited sampling MPA levels were drawn at 0, 40, and 240 minutes, and at 0, 40, and 120 minutes for FK and CSA patients, respectively. AUC was determined by averaging the results of two AUC methods: MLR (using R 2.9.7) and Bayesian kinetics (using NONMEM). MMF doses were adjusted using MPA AUC results, in conjunction with the patient evaluation of the attending transplant nephrologist.

MMF TDM is associated with a non-significant decreased rate of AR at 3 months. Power to detect differences between groups was not set for AUC monitoring. Six month AR for TDM patients not controlled for MMF manufacturer.

Discussion

MMF dose adjustment evaluation:

- Use of a narrow therapeutic index of 40-50 mg.hr/L may be too difficult to achieve, and a larger range may be indicated. Fifteen MPA levels during the course of the study indicated a dose change per protocol, but these were not completed as either the level was in the range of 30 to 60 mg.hr/L, and/or the incremental change of 250 mg per dose would have resulted in a level outside of range on the opposite end of the spectrum.
- The low rate of in-range AUC values on day 30 may indicate that more frequent AUC monitoring is needed between day 7 and day 30. Eight (31%) of the day 7 AUC levels prompted MMF decreases; 1 change was associated with a subtherapeutic AUC, while patients remained supratherapeutic on day 30. Two of 4 off-protocol dose changes (dose decreases for adverse effects without verification of AUC) contributed to AUC < 40 on day 30.

Outcomes:

- GI adverse effects were only measured on the days of AUC testing. Patients experienced adverse effects between testing days, but this data was not uniformly recorded and cannot be correlated to MPA levels.
- A significant decrease in WBC correlates to higher MMF doses utilized at day 7 in the TDM group. Patient groups appear to be evenly controlled for induction therapy, so this should not have influenced differences in leukopenia.

There may be a higher incidence of BK viruria associated with TDM. MMF doses averaged slightly higher in the TDM group at day 7 (possible overimmunosuppression), but lower at days 30 & 60. Three of 4 patients with viruria, also developed viremia.

- TDM is associated with a non-significant decrease in AR at both 8 weeks and 3 months. Power to detect differences between groups was not set a priori, and therefore this result may reflect a Type II error.
- There is no association between the use of TDM within the first 3 months and the incidence of rejection at 6 months. Patient care is returned to the referring nephrologist at 3 months, and medication protocol cannot be controlled. Eight of 23 TDM patients’ MMF dose was decreased within the period between 3 and 6 months. Two of these patients had biopsy proven rejection at 6 months.
- All patients may have their MMF dose decreased without increasing risk of AR, potentially decreasing patient costs and adverse drug effects.

Conclusions

- Evidenced by the low rate of in-range AUC values on day 30, more frequent AUC monitoring might be indicated during the first month post-transplant.
- The large proportion of MMF dose decreases on day 30 & 60 is consistent with literature that MPA AUC increases with time.
- Leukopenia may be associated with MMF TDM.
- Many patients can have their MMF dose decreased without increasing risk of AR.
- MMF TDM is associated with a non-significant decreased rate of AR at 3 months.
- Decreased rates of AR might be offset by increased rates of BK infection.

Contact Information

Ian C. Doyle, PharmD
Pacific University Oregon School of Pharmacy
Phone: 503-352-7371
Email: idoyle@pacificu.edu