Outcomes Associated with Mycophenolate Weight-Based Dosing in Varying Immunologic Risk Kidney Transplant Recipients

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PGY1 Pharmacy Resident

Disclosures

Amanda A.M. Al-Bahou, PharmD (speaker, primary investigator), has disclosed that she has no relevant financial disclosures. No one else in a position to control content has any financial relationships to disclose.

Lyndsey J. Bowman, PharmD, FAST, BCPS (planning committee, co-investigator), has disclosed that she serves on the Speakers’ Bureau for Veloxis Pharmaceuticals. She has no other relevant financial disclosures.

Allyssa Webb, PharmD, (co-investigator), has disclosed that she has no relevant financial disclosures. No one else in a position to control content has any financial relationships to disclose.

Meghan Bloxam, PharmD (planning committee, co-investigator), has disclosed that she has no relevant financial disclosures. No one else in a position to control content has any financial relationships to disclose.

Rajendra Baliga, MD (co-investigator), has disclosed that he has no relevant financial disclosures. No one else in a position to control content has any financial relationships to disclose.

Andrew J. Brueckner, PharmD, BCPS (planning committee, co-investigator), has disclosed that he has no relevant financial disclosures. No one else in a position to control content has any financial relationships to disclose.
Presentation Objective

Describe patient-specific variables that could influence clinical outcomes in kidney transplant recipients receiving mycophenolic acid products

Abbreviations

- **ARC**: acceptable reactive crossmatch
- **AUC**: area under the curve
- **BMI**: body mass index
- **BPAR**: biopsy-proven acute rejection
- **CMV**: cytomegalovirus
- **DGF**: delayed graft function
- **DM**: diabetes mellitus
- **IQR**: interquartile range
- **EC-MPS**: enteric-coated mycophenolate sodium
- **eGFR**: estimated glomerular filtration rate
- **GI**: gastrointestinal
- **HTN**: hypertension
- **KTR**: kidney transplant recipient
- **MMF**: mycophenolate mofetil
- **MPA**: mycophenolic acid
- **PRA**: panel reactive antibody
- **SD**: standard deviations
- **TDM**: therapeutic drug monitoring
Tampa General Hospital

Large academic medical center
- 1,007 beds
- Affiliated with USF Health Morsani College of Medicine
- Private, not-for-profit
- Level 1 trauma
- Solid organ transplant center
  - Ranked #6 in the nation for organ transplants by volume
  - 6 transplant pharmacotherapy specialists

Image Accessed at: https://www.linkedin.com/company/tampa-general-hospital

Background

Mycophenolate is a nucleotide blocking agent
- Maintenance immunosuppression post-transplant
  - Reduces rates of BPAR and increases survival
  - Used in >95% of KTRs
- Prescribed as fixed dosing in adult patients
  - MMF (Cellcept®) 2000 mg/day
  - EC-MPS (Myfortic®) 1440 mg/day


CellCept (mycophenolate mofetil) [package insert]. Nutley, NJ: Roche Laboratories Inc.
Myfortic (mycophenolate acid) [package insert], East Hanover, NJ: Novo Nordisk Pharmaceuticals Corporation.
MPA-Related Toxicities

- Most common MPA-related toxicities
  - Leukopenia
  - GI adverse effects
  - Infections
- Toxicities are often dose-dependent, leading to reductions, interruptions, or discontinuations
- Dose reductions increase the risk of BPAR and allograft failure by 2-fold

Reducing MPA-Related Toxicities

**Therapeutic Drug Monitoring of MPA products**

- Targeted therapeutic range: \( \text{AUC}_{0-12} \text{ hr} = 30 \text{ to } 60 \text{ mg*hr/L} \)
- Not routinely performed due to cost and feasibility
- Wang and colleagues showed no benefit of TDM in reducing treatment failure or adverse events

**TDM does NOT have any clinical benefit in reducing MPA-related adverse effects, but can we use other strategies focusing on patient-specific variables?**
### MPA Weight-Based Dosing

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Population</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Implications of Clinical MMF Dose According to Individual Body Weight in Japanese KTRs | • 43 Japanese patients
• Received renal transplant ≥6 months prior to study enrollment | • Mean MMF dose: 581 ± 207 mg/day
• Mean MPA AUC: 36.2 ± 18.7 mg*hr/mL
• Mean body weight: 56.3 ± 11.1 kg
• Rate of therapeutic MPA AUC of 74.7% with doses at 10-16 mg/kg/dose | • Lower body weights had higher AUC levels
• MMF dose based on total body weight of 10-16 mg/kg/dose can predict therapeutic levels
• Weight-based dosing could replace TDM |
| Is a standard fixed dose of MMF ideal for all patients? | • 53 Asian renal transplant recipients
• Received MMF for at least 3 months prior to study enrollment | • Positive correlation between AUC and body weight per MMF dose
• AUC of 45 mg*hr/L could be achieved with 12 mg/kg twice daily of MMF | • Fixed dosing may not be appropriate for all patients
• MMF should be dosed based on body weight |

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### Study Purpose

**Tampa General Hospital**

Utilizes FDA-approved fixed dosing of MPA products

Dose reductions based on toxicities and tolerability

**Study Aim**

Evaluate the efficacy and safety of a standardized MPA dosing schematic among varying immunologic risk KTRs
Methodology

Retrospective, single-center study of kidney transplant recipients

**Inclusion**
- Adult (≥18 years of age)
- Transplanted between January 1, 2015 to December 31, 2017
- Discharged on a MPA product

**Exclusion**
- Combined solid organ transplant
- Graft loss or death during index hospitalization
- Lost to follow-up within 3 months post-transplant

**Methodology**

- Patients were stratified based on immunologic risk and followed for 1-year

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Living related donor with 2 haplotype match&lt;br&gt;- OR zero antigen mismatches with no immunologic risk factors*&lt;br&gt;- OR age &gt;65 years old with no immunologic risk factors*</td>
<td>- Age ≤65 years old&lt;br&gt;- No immunologic risk factors*</td>
<td>- Any age&lt;br&gt;- Presence of one or more immunologic risk factors*</td>
</tr>
</tbody>
</table>

*Immunologic Risk Factors: repeat transplant, current PRA ≥20%, African American ≤65 years old, or positive ARC

- **MPA weight-based dosing**: low dosing (<20 mg/kg per day), standard dosing (20-33.9 mg/kg per day), and high dosing (≥34 mg/kg per day)
**Study Outcomes**

**Primary Outcome:** incidence of BPAR at 1-year post-transplant between high immunologic risk KTRs that received low doses of MPA compared to those that received standard and high doses at the time of discharge

**Secondary Outcomes**
- BPAR in low and moderate immunologic risk KTRs
- MPA-related adverse effects leading to dose reductions
- Number of MPA dose reductions
- MPA-related readmission rates
- Renal function (eGFR)
- Graft loss
- All-cause mortality

**Results**

Assessed for Eligibility (n=648)
- Met exclusion criteria
  - Combined solid organ transplant (n=72)
  - Graft loss on index hospitalization (n=12)
  - Lost to follow-up within 3 months (n=11)

Enrollment (n=553)
- Low Dosing (n=158)
- Standard Dosing (n=355)
- High Dosing (n=40)
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Low Dosing (n=158)</th>
<th>Standard Dosing (n=355)</th>
<th>High Dosing (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age in years (± SD)</td>
<td>55.2 (12.5)</td>
<td>53.4 (13.8)</td>
<td>45.7 (13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>121 (76.6)</td>
<td>201 (56.6)</td>
<td>13 (32.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, Black, n (%)</td>
<td>47 (29.7)</td>
<td>82 (23.2)</td>
<td>7 (17.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Indication for transplant, n (%)</td>
<td>36 (22.8)</td>
<td>68 (19.2)</td>
<td>6 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean BMI in kg/m² (± SD)</td>
<td>30.8 (4.9)</td>
<td>27.4 (4.6)</td>
<td>20.8 (3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DGF, n (%)</td>
<td>45 (28.4)</td>
<td>52 (14.7)</td>
<td>4 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceased Donor, n (%)</td>
<td>132 (83.5)</td>
<td>271 (76.3)</td>
<td>27 (67.5)</td>
<td>0.125</td>
</tr>
<tr>
<td>CMV High Risk, n (%)</td>
<td>40 (25.3)</td>
<td>65 (18.3)</td>
<td>7 (17.5)</td>
<td>0.386</td>
</tr>
<tr>
<td>Mean Cold Ischemia Time in hours (± SD)</td>
<td>781.4 (398.3)</td>
<td>724.9 (448.7)</td>
<td>618.6 (500.5)</td>
<td>0.093</td>
</tr>
<tr>
<td>Re-transplantation</td>
<td>12 (7.6)</td>
<td>40 (11.3)</td>
<td>9 (22.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Immunologic Risk, n (%)</td>
<td>7 (4.8)</td>
<td>151 (42.5)</td>
<td>23 (57.5)</td>
<td>0.292</td>
</tr>
</tbody>
</table>

## Concomitant Immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>Low Dosing (n=158)</th>
<th>Standard Dosing (n=355)</th>
<th>High Dosing (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction Immunosuppression, n (%)</td>
<td>129 (81.6)</td>
<td>283 (79.7)</td>
<td>33 (82.5)</td>
<td>0.574</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>0 (0)</td>
<td>5 (1.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>29 (18.4)</td>
<td>67 (18.9)</td>
<td>7 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Maintenance Immunosuppression at discharge, n (%)</td>
<td>150 (94.9)</td>
<td>351 (98.9)</td>
<td>40 (100)</td>
<td>0.011</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>83 (52.5)</td>
<td>166 (46.8)</td>
<td>22 (55)</td>
<td>0.354</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>1 (0.6)</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>0.767</td>
</tr>
<tr>
<td>Belatacept</td>
<td>7 (4.4)</td>
<td>3 (0.8)</td>
<td>0 (0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Average time to therapeutic tacrolimus level in days (± SD)</td>
<td>12.9 (39.5)</td>
<td>8.1 (5.3)</td>
<td>9.9 (11.5)</td>
<td>0.075</td>
</tr>
<tr>
<td>Average tacrolimus level in ng/mL over 1-year (± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>8.8 (2.6)</td>
<td>8.9 (4.2)</td>
<td>8.7 (2.4)</td>
<td>0.936</td>
</tr>
<tr>
<td>6 months</td>
<td>7 (2.6)</td>
<td>7.5 (4.8)</td>
<td>7.5 (2.2)</td>
<td>0.547</td>
</tr>
<tr>
<td>12 months</td>
<td>6.6 (1.8)</td>
<td>6.6 (2.2)</td>
<td>7.3 (2.9)</td>
<td>0.279</td>
</tr>
<tr>
<td>Maintenance Immunosuppression at 12 months, n (%)</td>
<td>125 (85.6)</td>
<td>284 (84)</td>
<td>33 (91.7)</td>
<td>0.736</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>126 (86.3)</td>
<td>312 (92.3)</td>
<td>35 (97.2)</td>
<td>0.033</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>80 (61)</td>
<td>214 (63.3)</td>
<td>22 (61.1)</td>
<td>0.155</td>
</tr>
<tr>
<td>Prednisone</td>
<td>7 (4.8)</td>
<td>12 (3.6)</td>
<td>0 (0)</td>
<td>0.628</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>9 (6.2)</td>
<td>7 (2.1)</td>
<td>1 (2.8)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

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Entire Study Population

Summary of Clinical Outcomes Among MPA Weight-Based Dosing Cohorts (n=553)

- BPAR: Low Dose (p=0.093), Standard Dose (p=0.615), High Dose (p=0.008)
- Readmission for GI Toxicity: Low Dose (p=0.615), Standard Dose (p=0.008), High Dose (p=0.218)
- Readmission for Leukopenia: Low Dose (p=0.008), Standard Dose (p=0.218), High Dose (p=0.008)
- Readmission for Infection: Low Dose (p=0.008), Standard Dose (p=0.218), High Dose (p=0.008)

Overall incidence of BPAR was low (8.5%)
Rate of BPAR was numerically higher in the low dosing cohort

High Immunologic Risk KTRs – Efficacy

Incidence of Efficacy Outcomes in High Immunologic Risk KTRs (n=242)

- BPAR: Low Dosing (p=0.029), Standard Dosing (p=0.209), High Dosing (p=0.13)
- AMR: Low Dosing (p=0.209), Standard Dosing (p=0.13), High Dosing (p=0.221)
- ACR: Low Dosing (p=0.209), Standard Dosing (p=0.13), High Dosing (p=0.221)
- De Novo DSA: Low Dosing (p=0.209), Standard Dosing (p=0.13), High Dosing (p=0.221)

Incidence of BPAR at 1-year was significantly higher in the low dose cohort (p=0.029)
Graft Survival at 1-Year Post-Transplant

Average time to BPAR at 1-year was shorter in low dose cohort (p=0.024)

High Immunologic Risk KTRs – Efficacy

High Immunologic Risk KTRs – Safety

<table>
<thead>
<tr>
<th>MPA-related readmissions, n (%)</th>
<th>Low Dosing (n=68)</th>
<th>Standard Dosing (n=151)</th>
<th>High Dosing (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI toxicity</td>
<td>17 (17.6)</td>
<td>22 (14.6)</td>
<td>4 (17.4)</td>
<td>0.823</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9 (13.2)</td>
<td>22 (14.6)</td>
<td>8 (34.7)</td>
<td>0.037</td>
</tr>
<tr>
<td>Infection</td>
<td>23 (33.8)</td>
<td>41 (27.2)</td>
<td>6 (26.1)</td>
<td>0.573</td>
</tr>
<tr>
<td>Any</td>
<td>31 (45.6)</td>
<td>59 (39.1)</td>
<td>11 (47.8)</td>
<td>0.547</td>
</tr>
</tbody>
</table>

Reason for first MPA dose reduction, n (%)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Low Dosing (n=68)</th>
<th>Standard Dosing (n=151)</th>
<th>High Dosing (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI intolerance</td>
<td>25 (36.8)</td>
<td>53 (35.1)</td>
<td>9 (39.1)</td>
<td>0.837</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27 (39.7)</td>
<td>58 (38.4)</td>
<td>8 (34.8)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>7 (10.3)</td>
<td>12 (7.9)</td>
<td>1 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Reducing immunosuppression</td>
<td>0 (0)</td>
<td>2 (1.3)</td>
<td>1 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Other/unidentified</td>
<td>2 (2.9)</td>
<td>2 (1.3)</td>
<td>1 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Average Number of MPA reductions (± SD)</td>
<td>2.3 (1.4)</td>
<td>2 (1.5)</td>
<td>2.3 (1.4)</td>
<td>0.295</td>
</tr>
</tbody>
</table>

Infection, n (%)

<table>
<thead>
<tr>
<th>Type</th>
<th>Low Dosing (n=68)</th>
<th>Standard Dosing (n=151)</th>
<th>High Dosing (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>36 (52.9)</td>
<td>73 (48.3)</td>
<td>11 (47.8)</td>
<td>0.579</td>
</tr>
<tr>
<td>Viral</td>
<td>18 (26.5)</td>
<td>51 (33.8)</td>
<td>8 (34.7)</td>
<td>0.534</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>3 (4.4)</td>
<td>4 (2.6)</td>
<td>0 (0)</td>
<td>0.528</td>
</tr>
</tbody>
</table>
Low and Moderate Immunologic Risk KTRs

No major differences in primary or secondary outcomes in low or moderate risk KTRs

MPA Dosing Over 1-Year

MPA doses gradually decline over 1-year in all immunologic risk groups. Low immunologic risk patients receive lower doses at all timepoints.
Clinical Implications

High Immunologic Risk Patients
- Low MPA weight-based doses increase the risk for BPAR
- MPA weight-based dosing is most relevant in this population

Low and Moderate Immunologic Risk Patients
- No major differences in efficacy or safety
- Lower MPA weight-based doses may be appropriate in low and moderate immunologic risk KTRs

Pharmacists’ Role
- MPA doses decline gradually over 1-year in all groups
- Inpatient and outpatient pharmacists can optimize MPA doses post-transplant

Study Limitations

- Retrospective and observational study design allows for unmeasured confounders
- BMI of the study population was relatively low
  - Median BMI = 27.7 kg/m² (IQR, 24-31.5 kg/m²)
  - Reduced the ability to capture effect of weight-based dosing in KTRs of extreme weights
- Plausible that subgroup analyses lacked power to detect a difference between groups
Summary

- Lower weight-based doses of MPA resulted in higher rates of BPAR in high immunologic risk KTRs
- No differences in outcomes based on MPA weight-based dosing in low or moderate immunologic risk KTRs
- Pharmacists can play a major role in optimizing MPA doses throughout the post-transplant period
- Further studies are needed to evaluate the optimal dose of MPA products in KTRs of extreme weights

Acknowledgements

Lyndsey J. Bowman, PharmD, FAST, BCPS
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Meghan Bloxam, PharmD
Rajendra Baliga, MD
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