Area Under the Curve Bioequivalence of Mycophenolate Mofetil: CellCept® vs Generic

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Abstract
Therapeutic drug monitoring (TDM) of mycophenolate mofetil (MMF) has been investigated using multiple linear regression (MLR) and bayesian pharmacokinetics (BAY) independently. Some studies have shown that therapeutic drug monitoring (TDM) of MMF via measuring area under the curve (AUC) may decrease risk of rejection as well as toxicity. Between May 2008 and June 2009, the FDA granted approval to 7 different manufacturers of generic MMF. Secondary to the between-patient and within-patient variability of MMF pharmacokinetics, it is important to use validated MLR and BAY models. These models have thus far been designed using only CellCept®. In this study, MLR and BAY models are used to evaluate the bioequivalence of mycophenolic acid (MPA) AUC of CellCept® (innovator MMF) compared to generic MMF (manufactured by Mylan) in renal transplant (RT) recipients. Four of 6 patients had generic MMF AUC levels within 90% - 110% AUC of innovator, and 5 of 6 patients had levels within 80 - 125%. Current MLR and BAY models might not be applicable to patients taking generic MMF.

Disciplines
Pharmacy and Pharmaceutical Sciences

Comments
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Abstract
Therapeutic drug monitoring (TDM) of mycophenolate mofetil (MMF) has been investigated using multiple linear regression (MLR) and bayesian pharmacokinetics (BAY) independently. Some studies have shown that therapeutic drug monitoring (TDM) of MMF via measuring area under the curve (AUC) may decrease risk of rejection as well as toxicity. Between May 2008 and June 2009, the FDA granted approval to 7 different manufacturers of generic MMF. Secondary to the between-patient and within-patient variability of MMF pharmacokinetics, it is important to use validated MLR and BAY models. These models have thus far been designed using only CellCept®. In this study, MLR and BAY models are used to evaluate the bioequivalence of mycophenolic acid (MPA) AUC of CellCept® (innovator MMF) compared to generic MMF (manufactured by Mylan) in renal transplant (RT) recipients. Four of 6 patients had generic MMF AUC levels within 90% - 110% AUC of innovator, and 5 of 6 patients had levels within 80 - 125%. Current MLR and BAY models might not be applicable to patients taking generic MMF.

Introduction
Mycophenolate mofetil is an immunosuppressant medication used to prevent rejection in kidney transplantation. The standard dose of MMF is 1000 mg twice daily. MMF undergoes enterohepatic recirculation, making it difficult to conduct TDM using peak and/or trough drug levels alone. MMF TDM using AUC may decrease risk of rejection as well as toxicity. AUC is estimated via limited sampling strategy with MLR or BAY pharmacokinetic models. These models are highly dependent on the pharmacokinetic properties of the innovator product, CellCept®. A generic product with significant absorption and distribution characteristics could not be used with current MLR and BAY models. The FDA approved 7 different generic forms of MMF between May 2008 and June 2009. The FDA awards a bioavailability rating (AB) to a drug if the manufacturer demonstrates that the generic product’s maximum concentration (Cmax) and AUC are both within 80-125% of the innovator. Only a small, single-dose study in healthy patients is required to demonstrate bioequivalence in both fasting and fed states, with a 90% confidence interval. It is unclear if bioequivalence would be determined in the renal transplant patient. We compare the AUCs of CellCept® vs. generic MMF (Mylan) in a fasting state using MLR and BAY models.

Methods
This study received approval from the Legacy Health System IRB. During the period of May 2009 to April 2010, we established an MMF TDM program utilizing MLR (using R 2.9.7) and Bayesian kinetics (using NONMEM). Six RT patients were prospectively enrolled in an non-randomized, open-label, crossover design study to compare MPA AUC of CellCept® to MPA AUC of a generic MMF formulation most often dispensed to our population (Mylan). Patients used the 250mg strength capsule of each product. Actual MMF doses varied at time of sampling as dictated by previous AUC monitoring. Limited-sampling of MPA levels were drawn at 0, 40, and 240 minutes for patients taking tacrolimus (FK) or sirolimus (SRL), or 0, 40, and 120 minutes for patients taking cyclosporine (CSA). Patients consumed a minimum of 6 days of drug following the crossover before the subsequent AUC was collected.

Results
The FDA has approved MMF 250 mg capsule (Mylan) as bioequivalent to CellCept®. Mylan compared their product to CellCept® in 32 fed and 34 fasting, healthy patients. Compared to that of CellCept® in the fasting state, Mylan reports their MMF product has an AUC infinity of 99%, AUC infinity of 92%, and Cmax of 92%. It is unclear if MMF (Mylan) reaches Cmax at the same time as CellCept® in RT patients, but is assumed to do so, as liberation of the drug is from a simple gelatin capsule. But, if not, AUC calculators using a specimen time for Cmax other than 40 minutes may be warranted.

Table 1: Patient renal function values on AUC measurement day

<table>
<thead>
<tr>
<th>Patient</th>
<th>CellCept® SCR mg/dL</th>
<th>CrCl ml/min</th>
<th>MMF (Mylan) SCR mg/dL</th>
<th>CrCl ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.03</td>
<td>51</td>
<td>1.11</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>0.99</td>
<td>59</td>
<td>0.98</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>0.91</td>
<td>55</td>
<td>0.89</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>1.11</td>
<td>65</td>
<td>1.24</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>1.32</td>
<td>52</td>
<td>1.27</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>0.98</td>
<td>79</td>
<td>0.97</td>
<td>81</td>
</tr>
</tbody>
</table>

*Cockcroft & Gault

Table 2: MMF AUC results, using 250 mg capsule increments

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>CNI</th>
<th>Post-op Day</th>
<th>AUC CellCept®</th>
<th>Post-op Day</th>
<th>AUC MMF (Mylan)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BAY</td>
<td>MLR</td>
<td>BAY</td>
</tr>
<tr>
<td>500 BID</td>
<td>FK</td>
<td>201</td>
<td>47.25</td>
<td>61.14</td>
<td>208</td>
</tr>
<tr>
<td>750 BID</td>
<td>FK</td>
<td>64</td>
<td>86.77</td>
<td>N/A*</td>
<td>71</td>
</tr>
<tr>
<td>1000 BID</td>
<td>CSA</td>
<td>57</td>
<td>38.67</td>
<td>39.77</td>
<td>64</td>
</tr>
<tr>
<td>500 BID</td>
<td>FK</td>
<td>67</td>
<td>28.86</td>
<td>35.18</td>
<td>74</td>
</tr>
<tr>
<td>1000 BID</td>
<td>FK</td>
<td>56</td>
<td>61.72</td>
<td>67.95</td>
<td>63</td>
</tr>
<tr>
<td>750 BID</td>
<td>SRL</td>
<td>82</td>
<td>28.52</td>
<td>35.16</td>
<td>76</td>
</tr>
</tbody>
</table>

*240-minute sample not available (broken in transit)

Discussion
Compared to the limited sampling strategy MLR and BAY AUC of CellCept®:

- 4 of 6 patients had generic MMF AUC levels within 90% - 110% AUC to that of the innovator, and 5 of 6 patients had levels within 80 - 125%. The number of patients included in this preliminary study is too small to perform any biostatistical confirmation. Additional RT patients should be evaluated to determine if these equivalency trends continue. It is unclear if the differences we see between generic MMF and innovator at day 60 will be exacerbated at time points closer to the surgical date when within-patient pharmacodynamics have more influence on AUC.

Table 2: MMF AUC results, using 250 mg capsule increments

Conclusions
MMF AUC monitoring is subject to a high degree of within-patient and between-patient variability. We report our results on a small sample of our patient population. It is unclear if the differences in AUC values between CellCept® and MMF (Mylan) are due to within-patient variability or true differences between the pharmacokinetic profiles of the 2 forms of MMF; which may limit the use of limited sampling AUC models. AUC bioequivalence testing for larger groups of RT patients is warranted. Current MLR and BAY models might not be applicable to patients taking generic MMF.

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