Therapeutic drug monitoring of cyclosporine versus mycophenolate mofetil in patients with renal failure and type II diabetes mellitus: Safety and efficacy

Rana Kamran Mahmood1,2, Syed Wasif Gillani1*, Muhammad Waqas Saeed3, Umar Ahmad1,4, Shabaz Mohiuddin Gulam1, Kishore Gana Sam1

1 College of Pharmacy, Gulf Medical University,  
2 ADCO Medical Centre Abu Dhabi,  
3 Rashid Hospital Dubai, DHA, UAE  
4 Sokoto state, Ministry of Health, Nigeria

Abstract—The purpose of this systematic review is to compare the safety and efficacy of the cyclosporine and mycophenolate mofetil in patients with diabetes and renal failure. There is no work we found that compare the safety and efficacy of cyclosporine and mycophenolate in diabetic and renal failure patients. Search was limited from 1983 to 2017 and articles must be in English. Articles searched from various resources and are evaluated using PRISMA. 25 articles selected and screened at the end 12 articles included in the study. The result shows that the pharmacokinetics of cyclosporine is affected by the renal failure and diabetes and mycophenolate did not show much variation in pharmacokinetics. The safety of mycophenolate in renal patient in term of serum Creatinine is more than the cyclosporine and shifting of patient from cyclosporine to mycophenolate shows better result. It is concluded that mycophenolate is more safe and efficacious than cyclosporine in diabetic patients with renal failure.

Keywords—type II diabetes, renal failure, autoimmune disorders, organ transplants, cyclosporine, mycophenolate mofetil, safety and efficacy, drug regimen, drug monitoring.

1. Introduction

A disease associated with the resistance of insulin and somewhat deficiency of insulin without damage of beta-cells of pancreas by autoimmunity is termed as type 2 diabetes mellitus1. It has observed around the globe the main cause of end stage renal disease and chronic renal failure is the type 2 diabetes [2]. Heart disease are also associated with the type 2 diabetes as it has observed people with type 2 diabetes are at double the risk of heart failure than people without type 2 diabetes [3].

It is estimated that prevalence of Chronic Kidney Disease (CKD) worldwide is 8 to 16 percent [4]. It is estimated that progression of chronic kidney disease to end stage renal disease can be prevented by adequate methods and techniques [5]. After the end stage renal disease the options left for the treatment are either dialysis (hemodialysis or peritoneal) or renal transplant [6].

After the end stage organ failure there is only one option left that is the organ transplantation. There is the need to protect the organ after transplantation from the body own immunity with Immunosuppressant [7]. Cyclosporine and mycophenolate mofetil are the immunosuppressant used in the organ transplantation. There is no data available that which one of cyclosporine and mycophenolate is more efficacious and safe in patients with type 2 diabetes and renal failure. The aim of this systemic review is to compare the safety and efficacy of cyclosporine and/or mycophenolate mofetil in patients with renal failure and type II diabetes mellitus patients.
2. Methods

2.1 SEARCH SUBJECTS
In this study, a required criterion is to search the literature as; patient with type-2 diabetes and renal failure using immunosuppressant for their organ transplant. Study the effect of type-2 diabetes and renal failure on safety and efficacy of cyclosporine and mycophenolate moftil.

2.2 SEARCH CRITERIA
Studies included in systematic review should fulfill the established criteria; published from 1983 to 2017 and should be in English. Search articles on type-2 diabetes and renal failure, with cyclosporine or mycophenolate in any type of organ transplantation. Exclude the articles of type-1 diabetes, cancer and multiple co morbidities patients.

2.3 SEARCH KEYWORDS
Type-2 diabetes, renal failure, autoimmune disorders, organ transplants, cyclosporine, mycophenolate, safety and efficacy, drug regimen, drug monitoring.

2.4 PRIMARY SEARCH
Different database and individual journal websites, like Pubmed, Google scholar, Microsoft academic, BASE.

2.5 SECONDARY SEARCH
Secondary search was focused mainly on reference articles, titles and abstracts. Articles that passed through primary screening were critically appraised for inclusion in the study analysis.

2.6 Rationale
There is no material we found for the safety and efficacy among Cyclosporine and Mycophenolate in renal and diabetic patient, which drug can affect the Pharmacokinetics and overall affect the patient health.

2.7 PRISMA
22 Articles searched out of which 5 were duplicated and removed, 2 are excluded with type-1 diabetes mellitus and 3 are not for the cyclosporine and mycophenolate typically. 3 more are excluded and searched again added 3 articles at the end 12 are included in the study with critical analysis.

3. Results and Discussion
Cyclosporine is eliminated by kidney in urine. As it is suggested from data collected from two articles shows failure increases the elimination time of cyclosporine from the body. Thus, cyclosporine stays for longer time in the body of renal failure patient than healthy individual [9, 11]. The above data shows that dosage adjustment is necessary for renal failure patients. Otherwise, high doses of cyclosporine may lead to toxicity. Iain A.M shows that in case of renal failure kidney is unable to eliminate the mycophenolic acid glucronide from the body. Thus the high Plasma Concentration of MPAG leads to the displacement of MPA from albumin thereby increasing the free MPA concentration in plasma [10, 13]. For patients with end stage renal failure the Creatinine clearance must be measured so that the dose of MPA can be adjusted as per the patient need. Fatemeh A khlaghi shows that cyclosporine metabolism is affected in the patients who have diabetes mellitus. In diabetic patients of kidney transplant the hepatic metabolism of cyclosporine is reduced due to the reduced activity of CYP450 3A12. Dosage adjustment must be done in such kind of patients; otherwise it may lead to cyclosporine toxicity. Chirag G Patel shows that there is not much difference in the concentration of
mycophenolic acid in diabetic and nondiabetic patients. So diabetes mellitus has no effect on the concentration of mycophenolic acid concentration dose of 720mg EC-MPS twice a day. It is evident from the graph 3, that reducing the dose of cyclosporine and shifting to mycophenolate in renal patient, serum Creatinine reduced and remain unchanged control group. Cyclosporine down titration to trough levels of 50–60 ng/ml after introduction of mycophenolate mofetil was shown to be a safe and effective strategy to improve chronic renal dysfunction in diabetic and non-diabetic heart transplant recipients across a wide range of Creatinine levels as shown in graph 5 and graph 6. We have seen that the efficacy and safety of Mycophenolate is better than the Cyclosporine as shown and effect of mycophenolate on the end stage renal disease are better than the cyclosporine [17]. We have also seen that the combination of Mycophenolate mofetil with Tacrolimus is better than the combination with the Cyclosporine [19].

**Figure 1:** schematic diagram shows the screening and eligibility of articles and 12 are critically analyzed

### 3.1 Effect of renal failure on cyclosporine

Author suggested that when cyclosporine g elimination half-life varies markedly between healthy participants and renal failure patients. Terminal half-life of cyclosporine G in healthy patients was approximately 5hrs whereas in renal failure patients it was almost 21 hrs. Similarly AUC of cyclosporine G between 0to 30hrs for healthy people was almost 8000mg but in renal failure the AUC varies markedly, but on average it was 7000mg9 as it is evident from the table 1.In another article cyclosporine concentration was noted in four patients mean 3rd half live 15.7 hr was longer than 1sthalf life 1.08 hrs11.

Cyclosporine is eliminated by kidney in urine. As it is suggested from data collected from two articles shows
failure increases the elimination time of cyclosporine from the body. Thus, cyclosporine stays for longer time in the body of renal failure patient than healthy individual. The above data shows that dosage adjustment is necessary for renal failure patients. Otherwise, high doses of cyclosporine may lead to toxicity.

**Table 1.** Patients with renal failure taking oral or intravenous cyclosporine in renal and healthy patients. AUC from 0-30hrs, an AUC normalized to 1 mg dose

<table>
<thead>
<tr>
<th>Name of articles</th>
<th>Condition of patients (no. of patients)</th>
<th>Average AUC (mg)</th>
<th>Average half-life 3:1 (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic of Cyclosporine G IV in patient with renal failure</td>
<td>Patients with healthy kidneys (2) 3.2mg/kg</td>
<td>8237.5</td>
<td>5.2 : 0.058</td>
</tr>
<tr>
<td></td>
<td>Patients with renal failure (6) 3.2mg/kg</td>
<td>8385.5</td>
<td>18.9 : 0.137</td>
</tr>
<tr>
<td>Pharmacokinetic of Cyclosporine G ORAL in patient with renal failure</td>
<td>Patients with healthy kidneys (2) 600mg</td>
<td>7506.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with renal failure (2) 600mg</td>
<td>4558.5</td>
<td></td>
</tr>
<tr>
<td>Intravenous cyclosporine kinetics in renal failure</td>
<td>Patients with renal failure</td>
<td>47.2 $^a$</td>
<td>15.7</td>
</tr>
</tbody>
</table>

### 3.2 Effect of renal failure on the concentration of mycophenolate

Iain A.M took comparison of mycophenolic acid the active form of mycophenolate mofetil and mycophenolate glucuronide a metabolite of MPA that is eliminated from the body. In table 2 it is mentioned that MPA mean AUC is 55.7mg/l.hr and half-life is 0.66hr whereas MPAG concentration is 1565mg/l.hr and half-life is 2hr in renal failure.

It is evident from the study, the competition of MPA and MPAG binding to albumin in case of renal failure. As it is shown in table 2 that the average AUC of MPA is 37.5mg/l.hr and AUC of MPAG is 241.8 mg/l.hr.

Iain A.M shows that in case of renal failure kidney is unable to eliminate the mycophenolic acid glucuronide from the body. Thus the high Plasma Concentration of MPAG leads to the displacement of MPA from albumin thereby increasing the free MPA concentration in plasma.

For patients with end stage renal failure the Creatinine clearance must be measured so that the dose of MPA can be adjusted as per the patient need.

### 3.3 Effect of diabetes on cyclosporine concentration

Fatemeh A khlaghi suggested in the study that diabetes mellitus affects the metabolism of cyclosporine by CYP450 3A. Diabetes reduces the CYP450 3A activity. Four metabolites of cyclosporine concentrations were measured in diabetic and non-diabetic kidney transplant patients. The shows that post absorption blood concentration of cyclosporine metabolites were almost half in diabetic patients than that in non-diabetic patients. Table 3 shows the concentration of cyclosporine metabolites during absorption and post absorption phase.

Fatemeh A khlaghi shows that cyclosporine metabolism is affected in the patients who have diabetes mellitus. In diabetic patients of kidney transplant the hepatic metabolism of cyclosporine is reduced due to the reduced activity of CYP450 3A12. Dosage adjustment must be done in such kind of patients; otherwise it may lead to cyclosporine toxicity.
Table 2: shows the pharmacokinetic study of mycophenolate in healthy and renal failure patients.

<table>
<thead>
<tr>
<th>Name of article</th>
<th>AUC (0-36) of MPA</th>
<th>AUC (0-36) of MPAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics of mycophenolate mofetil in patients with end-stage renal failure</td>
<td>55.7mg/l.hr</td>
<td>1565mg/l.hr</td>
</tr>
<tr>
<td>The Effect of Renal Insufficiency on Mycophenolic Acid Protein Binding</td>
<td>37.5mg/l.hr</td>
<td>241.8 mg/l.hr</td>
</tr>
<tr>
<td>Pharmacokinetics of mycophenolate mofetil in healthy patients. Oral</td>
<td>73.9 (0-24)</td>
<td>332(0-24)</td>
</tr>
<tr>
<td>Pharmacokinetics of mycophenolate mofetil in healthy patients. IV</td>
<td>86.2 (0-24)</td>
<td>285(0-24)</td>
</tr>
</tbody>
</table>

Table 3: shows the difference cyclosporine metabolite in absorption and postabsorption phase in diabetic and nondiabetic patients.

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Absorption Phase (&lt; 3 hour after dose)</th>
<th>Post-absorption Phase (≥3 h after dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-diabetic</td>
<td>Diabetic</td>
</tr>
<tr>
<td>AM1</td>
<td>19.1</td>
<td>19.0</td>
</tr>
<tr>
<td>AM9</td>
<td>12.5</td>
<td>14.4</td>
</tr>
<tr>
<td>AM4N</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>AM1c</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>AM19</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>AM1c9</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

3.4 Effect of diabetes mellitus on mycophenolate:

Chirag G Patel expresses that total mycophenolic acid initial concentration was high in diabetic patients than nondiabetic patients. Graph 1 show that the initial concentration at time 0 was 3.3 mg/L in diabetic patients while nondiabetic patients the concentration at time 0 was 2.3mg/L. But the Cmax in diabetic patients was 18.1mg/L and in nondiabetic was 22.2mg/L. Tmax was also low for diabetic patients which is 1.8hr as compared to nondiabetic patients where Tmax was 2.1hr. Study also shows AUC from time 0 to 12 hrs was 73.5mg/L.hr in diabetic patients whereas in nondiabetic patients 69.8mg/L.hr.

Chirag G Patel shows that there is not much difference in the concentration of mycophenolic acid in diabetic and nondiabetic patients. So diabetes mellitus has no effect on the concentration of mycophenolic acid concentration dose of 720mg EC-MPS twice a day.

4. CONCENTRATIONS VARIATIONS BETWEEN MYCOPHENOLATE & CYCLOSPORINE WHEN ADMINISTERED TOGETHER

Aurelija Noreikait discusses the effect of cyclosporine on the plasma concentration of mycophenolate mofetil. The study showed that increasing the dose of cyclosporine increases the plasma concentration of mycophenolate in plasma whereas cyclosporine at low doses reduced the mycophenolate mofetil concentration. Three different groups were created in group 1, 1000mg mycophenolate mofetil was administered and cyclosporine doses was given ranging from 180mg to 240mg. in group 2, mycophenolate dose was 2000mg but the cyclosporine range was same i.e. 180mg to 240mg. in group 3, mycophenolate was increased to 3000mg but the cyclosporine range was again 180mg to 240mg8. It is evident from the graph 2 shows that co administration of cyclosporine and mycophenolate decreases the AUC and C max.
Graph 1: shows the difference of pharmacokinetic parameters in diabetic and non-diabetic patients.

Graph 2: shows the co administration of cyclosporine and mycophenolate effects pharmacokinetics of mycophenolate mofetil.

5. Effect of mycophenolate on renal failure when cyclosporine is reduced

Christiane E. Angermann that in intervention group of patients getting mycophenolate mofetil at constant plasma concentration, the reduction of cyclosporine concentration was done from 70ng/ml to 57 ng/ml, while in control group the cyclosporine was reduced to 116ng/ml. It can be suggested that serum creatinine reduced from 210.2µmol/L to 186.8µmol/L in intervention groups but in controlled groups remained unchanged.

It is evident from the graph 3, that reducing the dose of cyclosporine and shifting to mycophenolate in renal patient, serum Creatinine reduced and remain unchanged control group.
Graph3: shows that serum Creatinine level in patients with renal failure and control.

6. Safety and Efficacy Analysis

Omer A. Raheem shows the mycophenolate effect on the end stage renal disease in the article17 as it is shown in the graph4.

Graph4: the effect of MMF on End Stage Renal Disease

Omer A. Raheem shows the comparison among the patient change from cyclosporine to MMF (intervention) and patient remain on treatment of Cyclosporine (Control) improve chronic renal dysfunction in Heart Transplant patient. We can see the difference in values of Creatinine Clearance and Glucose is as follows17. It is evident from the graph 5 that serum Creatinine is reduced from 210 to 186 in intervention change from cyclosporine to mycophenolate moftil and a slight change in HbA1c. It is concluded that mycophenolate is safer in renal patient than cyclosporine.
Graph 5: shows change in Serum Creatinine from the 1 month to 8 months in Control and intervention group elaborate the safety

Graph 6: shows the change in serum concentration as down titration of cyclosporine and shifted to mycophenolate

It is shown that cyclosporine down titration to trough levels of 50–60 ng/ml after introduction of mycophenolate mofetil was shown to be a safe and effective strategy to improve chronic renal dysfunction in diabetic and non-diabetic heart transplant recipients across a wide range of Creatinine levels as shown in graph 5 and graph 6.

He‘lio Tedesco Silva shows the comparison of combination of MMF with tacrolimus and cyclosporine and compares the results for the safety and efficacy and shows the patient survival with mycophenolate and
tacrolimus (group 1) is 93.2% than cyclosporine plus mycophenolate (group 2) is 92.5% and graft survival is also significantly higher in group 1 than group 2 [19]. As it is shown in graph 7.

Graph 7: shows the difference of patient survival and graft survival in patients with group 1 medication and group 2 medications.

We have seen that the efficacy and safety of Mycophenolate is better than the Cyclosporine as shown and effect of mycophenolate on the end stage renal disease are better than the cyclosporine [17]. We have also seen that the combination of Mycophenolate mofetil with tacrolimus is better than the combination with the Cyclosporine [19].

7. Conclusion

It is suggested that the cyclosporine pharmacokinetic in renal failure and diabetic patient have shown that there is need to adjust dose of cyclosporine more than the mycophenolate. Little dose of mycophenolate adjustment need only in case of renal failure in diabetes mellitus no need to adjust the dose while in case of Cyclosporine there is need to adjust the dose for both of the cases in renal failure and diabetes. Safety profile of mycophenolate is better than the cyclosporine in patients with type-2 diabetes and renal failure.

8. References


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