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IMPACT OF THE USE OF TACROLIMUS VERSUS CYCLOSPORINE ON CYTOMEGALOVIRUS COLITIS AND HEPATITIS IN POST RENAL TRANSPLANT PATIENTS

By
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Abstract

Cytomegalovirus (CMV) is a common viral infection after kidney transplantation (KT). Major risk factors for CMV infection include the overall immunosuppression intensity and the CMV serostatus. The study compared the use of Tacrolimus versus Cyclosporine on the incidence of cytomegalovirus (CMV) colitis and hepatitis in post renal transplant patients. This was a retrospective cohort study; in which 90 adult post renal transplant Egyptian patients were divided into 2 groups: G1: 45 patients on Tacrolimus, mycophenolate, steroids. G2:45 patients on Cyclosporine, mycophenolate, steroids.

The results showed insignificant difference between both groups as to incidence of CMV colitis and hepatitis in positive CMV/PCR patients post renal transplantation with P value (0.659) (1.000). However, the incidence of CMV infection significantly increased with the increase of trough level of immunosuppressive agent whether tacrolimus or cyclosporin.

Keywords: Immunosuppressant, Cytomegalovirus infectious disease, Kidney Transplantation.

Introduction

Human cytomegalovirus belongs to the viral family known as herpesviruses, Herpesviridae, or human herpesvirus-5 (HHV-5). Infection with Cytomegalovirus (CMV) may be asymptomatic in healthy individuals, but it can be life-threatening in immunocompromised patients (Gupta and Shorman, 2020). A well-recognized complication following solid organ transplant is invasive cytomegalovirus (CMV) disease but, infrequently reported to cause significant small bowel pathology (Helmick and Agbim, 2019).

Gastrointestinal tract infection with cytomegalovirus (CMV) is attributed to reactivation of dormant CMV due to immunosuppression and is rarely due to superinfection of diseased gastrointestinal tract. CMV can infect any part of the gastro-intestinal system from esophagus to rectum, but commonly involves colon (55%), esophagus and stomach (40%) and less commonly small intestine (Kothari *et al,* 2021).

Generally, tissue-invasive disease of liver in relatively immunocompromised patients is like that in mononucleosis-like syndrome except for the more prominent jaundice and higher levels of liver enzymes. Rare cases of fulminant hepatic failure secondary to CMV were reported (Fakhreddine *et al,* 2019).

Calcienurin inhibitors (CNIs) such as cyclosporine and tacrolimus are the mainstay of immunosuppression in kidney transplantation. Graft survival rates have improved significantly as a result of advancements in the field of renal transplantation and developments in immunosuppressive medication (Toda *et al,* 2015). Tacrolimus in particular improved the allograft function with fewer rejections compared to other regimens. But, the tacrolimus may be associated with higher complications than those on Cyclosporine (Ong *et al,* 2020). Calcineurin inhibitors increased the CMV risk by inhibiting specific memory T cells (Bestard *et al,* 2012).

This study aimed to compare the impact of Tacrolimus® versus Cyclosporine® on the incidence patients of cytomegalovirus (CMV) colitis and hepatitis in post renal transplant patients.

Subjects and Methods

This retrospective cohort study was done

in Ain Shams University Hospitals' outpatients database from January 2017 to December 2020. The study included 90 adult post renal transplant patients who received Calcineurin inhibitors (Tacrolimus or cyclosporine), mycophenolate and prednisone and followed up for 6 months. Patients were divided into 2 groups of 45 each. G1: On Tacrolimus, mycophenolate, steroids, & G2: On cyclosporine, mycophenolate, steroids.

Inclusion criteria: Adult renal transplant recipients' patients aged from 18 to 60 years old received Calcineurin inhibitors immunosuppression (Tacrolimus or Cyclosporine).

Patients with diabetes mellitus, HCV, HBV, or HIV and/or with Cytomegalovirus sero-positive or on other immunosuppressive regimens were excluded.

All patients were subjected to medical history taking including immunosuppressive therapy, any liver disease, diabetes mellitus, cause of renal failure, previous transplantation, severity of underlying disease (Renal failure), and hemodialysis as well as admission to intensive care unit; donor-recipient matched; corticosteroid, antibiotic, or antifungal therapy; donor age; and presence of infection, comprehensive physical examination and clinical assessment of patients for signs and/or symptoms of colitis (abdominal pain, diarrhea, bleeding per rectum).

Laboratory examinations: Pre-renal transplantation, donors and recipients were examined for CMV/IgM, CBC, ALT, AST, fasting blood glucose, post prandial blood glucose, HBA1c and pelvi-abdominal ultrasound, total & direct bilirubin, HBA1c, hepatitis B surface Antigen (HBsAg), HCV, and HIV Antibody. Post renal transplantation, the recipients were examined for CMV/IgM, & PCR. The positive ones were examined for colitis, hepatitis, ALT, AST, CBC, serum creatinine, estimated GFR and tacrolimus and cyclosporine level.

Patients who developed gastrointestinal symptoms suggestive for colitis or elevated hepatic transaminases with positive CMV/PCR with clinical and/or serologic response to Ganciclovir® or Valganciclovir® treatment were defined as CMV colitis and hepatitis respectively.

Ethical considerations: The study was approved by the Ethics Committee, Faculty of Medicine, Ain Shams University (Reference No.: MD 162/2021), which agreed with Helsinki Declaration (2013). There were adequate confidentiality of patients' data, and none had right to read medical information except the study purpose. Patients' privacy was maintained in all published and written data resulting from the study.

Statistical analysis: Data were computerized and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described as number and percent. The Shapiro-Wilk test verified the normality of distribution quantitative data as (minimum & maximum), mean, standard deviation, median and interquartile range (IQR). Significance of results was judged at the 5% level. The Chi-square test compared between different groups, Student t-test compared between two groups, and Paired t-test compared between two periods.

Results

G1: Patients on Tacrolimus, mycophenolate, steroids, 20 females and 25 males with ages ranged between 38.44 & 51.42 years (45.61±3.16). G2: Patients on cyclosporine, mycophenolate, steroids, 19 females and 26 males with ages ranged between 35.04 & 56.24 years (45.64±5.04), but without significant differences.

CBC parameters in pre and post-transplant settings showed a significantly lower WBC and platelet count in (G2) in pre-transplant settings with P=0.021* &0.008* respectively. G1 showed a significant difference between patients in pre and post-transplant settings as to Hb and platelet count (P <0.001* & 0.001* respectively). G2 showed a significant difference between patients in pre- and post-transplant settings as to WBC count, Hb and platelet count (P<0.007*, <0.001* and <0.001* respectively). Patients in both

groups neither differed in pre- nor in post-transplant as to ALT, AST, total & direct bilirubin.

As to the CMV in post-transplant setting, 22 patients in G1 had positive IgM and 10 with positive PCR versus 21 patients in G2, and 11 positive PCR without a significant difference.

Colitis evidenced by diarrhea was among 15 patients in G1, 10 of them showed a positive CMV/PCR, but in G2, 16 patients developed colitis 11 of them showed positive PCR without a significant difference. Moreover, the incidence of hepatitis as evidenced elevated transaminases post-renal transplant in G1 was reported in 26 patients, 5 of them had a positive CMV PCR. While in G2 hepatitis was reported in 17 patients, 5 of them also showed a positive CMV PCR. There was significant difference between groups as to incidence of CMV hepatitis.

The incidence of CMV induced acute graft rejection was also observed in both groups where in G1, 16 patients had graft rejection out of them 4 patients turned to have CMV induced rejection versus 12 patients in G2 out of them 3 patients turned to have CMV induced acute rejection. There was no significant difference between both groups as to CMV incidence induced acute graft rejection. Incidence of both CMV colitis and hepatitis was not affected with immunosuppressive regimen (tacrolimus or cyclosporin). There was a high significant difference between trough level of immunosuppressive agent and CMV (PCR positivity). G1 patients with positive CMV/PCR had tacrolimus trough levels were between 8.6-12ng/ml (10.67± 1.17), but negative ones had tacrolimus trough levels ranged between 4.1-9ng/ml (7.62 ±1.36) with a high significant difference (P = 0.000).

ROC curve showed a cut off trough level of tacrolimus more than 9ng/ml as a high risk for CMV infection with 90% sensitivity and 100% specificity. Patients on cyclosporine regimen and developed CMV infection had significantly higher trough levels than negative CMV/PCR, ranged between 280-510ng/ml (406.36±61.85) for PCR positive patients versus 100-300ng/ml (245± 45.81) for PCR negative ones (P=0.000). ROC curve showed a cut off trough level of cyclosporine more than 300ng/ml as a high risk for CMV with 90.91% sensitivity and 100% specificity.

Details were given in tables (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 & 12) and figures (1 & 2).

Table 1: Comparison between groups as to CBC

Items	CBC	G1 (n= 45)	G2 (n= 45)	t	P value
WBCs (x10³ /ml³)	Pre				
	Min. – Max.	4.0 – 9.0	3.0 – 8.0	2.345*	0.021*
	Mean ± SD.	6.51 ± 1.22	5.96 ± 1.02		
	Post				
	Min. – Max.	5.0 – 11.0	4.0 – 9.0	1.516	0.133
	Mean ± SD.	7.07 ± 1.62	6.60 ± 1.29		
	p_1	0.085	0.007*		
Hb (g/dl)	Pre				
	Min. – Max.	8.25 – 15.22	9.79 – 15.88	1.931	0.057
	Mean ± SD.	12.16 ± 1.39	12.69 ± 1.23		
	Post				
	Min. – Max.	9.86 – 18.14	11.25 – 18.37	0.719	0.474
	Mean ± SD.	14.35 ± 1.60	14.58 ± 1.50		
	p_1	<0.001*	<0.001*		
Platelet (x10³ /ml³)	Pre				
	Min. – Max.	246.0 – 293.0	219.0 – 307.0	2.703*	0.008*
	Mean ± SD.	271.60 ± 11.17	262.87 ± 18.58		
	Post				
	Min. – Max.	247.0 – 314.0	246.0 – 310.0	0.805	0.423
	Mean ± SD.	282.80 ± 15.72	280.07 ± 16.50		
	p_1	0.001*	<0.001*		

Table 2: Comparison between groups as to laboratory investigations

Items	Laboratory examinations	G1 (n= 45)	G2 (n= 45)	t	P value
AST (U/L)	Pre				
	Min. – Max.	1.27- 30.22	3.66-33.64	1.369	0.175
	Mean ± SD.	15.95±6.56	17.80±6.29		
	Post				
	Min. – Max.	8.68- 23.98	8.75- 23.99	0.369	0.713
	Mean ± SD.	16.33±3.22	16.58±2.98		
	p_1	0.723	0.262		
ALT(U/L)	Pre				
	Min. – Max.	1.60- 35.44	3.23- 38.03	0.591	0.556
	Mean ± SD.	19.60±7.35	18.67±7.52		
	Post				
	Min. – Max.	8.05- 20.49	2.98- 42.63	1.677	0.100
	Mean ± SD.	15.64±2.49	17.99±9.06		
	p_1	0.001*	0.672		
Total-Bilirubin (µmol/L)	Pre				
	Min. – Max.	3.03- 15.83	4.97- 17.15	0.363	0.718
	Mean ± SD.	10.77±3.36	10.52± 3.08		
	Post				
	Min. – Max.	1.63- 15.14	2.35- 16.77	1.622	0.108
	Mean ± SD.	9.09±3.06	10.18±3.31		
	p_1	0.013*	0.600		
Direct Bilirubin (µmol/L)	Pre				
	Min. – Max.	1.18- 13.14	0.77-13.54	0.405	0.687
	Mean ± SD.	6.90±2.62	7.13±2.87		
	Post				
	Min. – Max.	2.68- 14.53	0.47- 13.18	0.242	0.809
	Mean ± SD.	7.60 ±2.34	7.72±2.55		
	p_1	0.184	0.306		

Table 3: Comparison between groups as to CMV serology post renal transplantation

CMV IgM	G1 (n = 45)		G2 (n = 45)		χ^2	P value
	No.	Percent	No.	Percent		
Negative	15	33.3%	14	31.1%	0.280	0.869
Positive	22	48.9%	21	46.7%		
Equivocal	8	17.8%	10	22.2%		

Table 4: Comparison between CMV IgM positive patients among groups as to CMV PCR:

CMV PCR	G1 (n = 45)		G2 (n = 45)		χ^2	P value
	No.	Percent	No.	Percent		
Negative	12	54.5%	10	47.6%	0.206	0.650
Positive	10	45.5%	11	52.3%		

Table 5: Comparison between groups as to colitis post renal transplantation

Colitis	G1 (n = 45)		G2 (n = 45)		P value
	No.	Percent	No.	Percent	
Negative	30	66.7%	29	64.4%	0.824
Positive	15	33.3%	16	35.6%	

Table 6: Comparison between groups as to incidence of hepatitis post renal transplantation

Hepatitis	G1 (n = 45)		G2 (n = 45)		P value
	No.	Percent	No.	Percent	
Negative	19	42.2%	28	62.2%	0.058
Positive	26	57.8%	17	37.8%	

Table 7: Comparison between groups as to acute rejection post renal transplantation

Acute rejection	G1 (n = 45)		G2 (n = 45)		χ^2	P value
	No.	Percent	No.	Percent		
Negative	29	64.4%	33	73.3%	0.829	0.362
Positive	16	35.6%	12	26.7%		

Table 8: Comparison between positive CMV/PCR patients as to CMV colitis, hepatitis colitis, hepatitis & acute rejection

Positive CMV PCR	G1 (n = 45)		G2 (n = 45)		P value
	No.	Percent	No.	Percent	
Colitis	10	100.0%	11	100.0%	–
Acute rejection	4	40.0%	3	27.3%	FEp=0.659
Hepatitis	5	50.0%	5	45.5%	FEp=1.000

Table 9: Relationship between positivity of CMV PCR and Tacrolimus trough blood level in G1 post renal transplantation.

Drug level	Negative CMV PCR (n= 35)	Positive CMV PCR (n=10)	Test value	P-value	Sig.
Mean ±SD	7.62±1.36	10.67±1.17	-6.435•	0.000	HS
Range	4.1- 9	8.6-12			

Table 10: ROC curve to predict Tacrolimus Trough level caused positive CMV -PCR among G1

Cut off point	AUC	Sensitivity	Specificity	Positive PV	Negative-PV
>9 (ng/ml)	0.977	90.00	100.00	100.0	97.2

Table 11: Relationship between positive CMV/PCR & trough Cyclosporine blood level in post renal transplantation

Drug level	Negative CMV PCR (n= 34)	Positive CMV PCR (n=11)	Test value	P value	Sig.
Mean ± SD	245 ± 45.81	406.36 ± 61.85	-9.304•	0.000	HS
Range	100 – 300	280 – 510			

Table 12: ROC curve to predict cut off cyclosporine trough level caused positive CMV PCR among G2

Cut off point	AUC	Sensitivity	Specificity	Positive PV	Negative-PV
>300(ng/ml)	0.979	90.91	100.00	100.0	97.1

Discussion

Generally, Cytomegalovirus (CMV) is a wide-spread virus, with manifestations range from asymptomatic to severe end-organ dysfunction in immunocompromised patients with congenital CMV disease (Mozaffar *et al,* 2018). CMV is the main infectious agent causative of morbidity and mortality in transplant recipients (de Matos *et al,* 2017). In patients with a depressed immune system, CMV is more aggressive causing CMV hepatitis which may lead to fulminant liver failure, Cytomegalovirus retinitis characterized by a "pizza pie appearance" on ophthalmic exam, CMV esophagitis, Cytomegalovirus colitis, CMV pneumonitis, Polyradiculopathy, Transverse myelitis, and Subacute encephalitis (Taylor, 2023).

The CMV risk factors in kidney transplant recipient were recipients' age, donor positive CMV antibodies/recipient negative CMV antibodies status and the net state of immunosuppression as well as the management of kidney recipients in post-transplant period (Al Atbee and Tuama, 2022). Without the effective preventive strategies, approximately 60% of kidney transplant recipients experienced active CMV infection, and approximately 20% developed CMV disease (Sagedal *et al,* 2000). People with CMV may pass the virus in their body fluids, such as saliva, urine, blood, tears, semen, and breast milk. CMV is spread from an infected person in the following ways: 1- From direct contact with saliva or urine, especially from babies and young children, 2- Through sexual contact, 3- From breast milk to nursing infants, and 4- Through transplanted organs and blood transfusions (CDC, 2020).

Gastrointestinal tract affection CMV infection is usually due to reactivation of a dormant CMV after immunosuppression most commonly affects the colon, esophagus and stomach but rarely small intestine (Kothari *et al,* 2021). In healthy individuals, CMV colitis is usually asymptomatic or causes self-limited disease, but can result in chronic infection or a life-long carrier state with intermittent reactivation, but reactivation is frequent in severe or corticosteroid-resistant ulcerative colitis (Karigane *et al,* 2014).

In the present study, the patients' aged and sexes were cross matched as well as in the causes of renal failure. Besides, in the present study, the incidence of CMV colitis and hepatitis didn't show significantly difference among both groups indicating that the immunosuppressive regimen (whether tacrolimus or cyclosporine based) were effective. This agreed with Ong *et al.* (2020), they reported

that the overall rate of CMV infection didn't differ between patients on tacrolimus and on cyclosporine. Nevertheless, more patients on tacrolimus were admitted with a primary diagnosis of infection compared to cyclosporine (55.0% vs. 30.6%, P=0.004). But, this result disagreed with San Juan *et al.* (2008), who enrolled 1470 renal transplanted patients 16 of them were on cyclosporine but not Tacrolimus was independently related to an increased risk of CMV. The explanation for such differences between both calcineurin inhibitors remains uncertain. Tacrolimus is known to be 30-100 times more potent than cyclosporine in vitro, but peak in vivo calcineurin activity inhibition is greater with cyclosporine led to a higher effect in T cell function (Sallustio, 2021). On the contrary, Kizilbash ***et al.*** (2018) on pediatric population, found a significantly higher incidence of CMV infection among the recipients who received tacrolimus as compared to those on cyclosporine.

In the present study, the acute rejection showed insignificant difference among both groups (^{FE}p=0.659). This agreed with Ravanshad *et al.* (2020), who reported that Tacrolimus was insignificantly superior to cyclosporine regarding incidence of acute rejection in pediatric population (RR= 0.79, 95% CI: 0.59-1.05; P > 0.05). Also, in the present study, CMV incidence of infection was related to the trough level of tacrolimus and cyclosporine in both groups with a highly significant relation. CMV infected patients had significantly higher trough levels of tacrolimus (10.67±1.17ng/ml) compared to CMV/PCR negative ones (7.62±1.36ng/ml), P= 0.000. Also, CMV infected patients had significantly higher trough levels of cyclosporine (406.36±61.85ng/ml) compared to CMV/ PCR negative ones (245±45.81ng/ml), P= 0.000. This agreed with Percy *et al.* (2017), who carried out retrospective cohort study on 77 renal transplant recipients reported recurrences due to acute infections, out of them 27% had CMV infection. Besides, patients admitted (35%) had higher tacrolimus trough levels upon, which could recommend a correlation between the infection incidence and tacrolimus trough levels. Also, this agreed with Asadzadeh *et al.* (2023), who reported that among 58 renal transplant patients given high dosage with a higher level of cyclosporine caused increased susceptibility to CMV infections.

In the present study, a cut off trough level of tacrolimus was more than 9ng/ml indicating high risk for CMV infection in G1 with 90% sensitivity and 100% specificity. This agreed with Jouve *et al.* (2018), who reported that early as well as for long term trough tacrolimus level (5-7ng/ml) prevented some CMV complications. Also, the result agreed with Rao *et al.* (2020), who reported that genetic polymorphism effects the tacrolimus dose requirement. Enzyme expressor (AA) is associated with low C/D ratio and higher risk of acute rejection. Heterozygous (AG) and non expressors (GG) are at higher risk of developing tacrolimus related nephrotoxicity and infections. ABCB1 polymorphisms have no significant impact on tacrolimus C/D ratio. They added that tacrolimus related complications can be predicted prior to renal transplant by analyzing CYP3A5 genetic polymorphisms and doses can be adjusted in order to prevent the complications.

In the present study, the cut off trough level of cyclosporine was more than 300ng/ml indicating the increased in CMV infection risk among patients and that regimen of immunosuppression didn't significantly affect the incidence of CMV colitis and hepatitis in both study groups. But, the CMV incidence of infection significantly increased with the in-creased trough level of immunosuppressive agent (tacrolimus or cyclosporine). This agreed with Einollahi (2012), they reported that the CMV rate of infection was higher in the first six months post transplantation in recipients with the higher cyclosporine level (P<0.001) with a mean trough level of 267± 134ng/ml in CMV infected patients versus 187±121ng/ml) in control (P< 0.001). Also,

this result agreed with Ragab *et al.* (2013), they on retrospective study from 102 renal transplanted patients found that concentrations of cyclosporine trough levels ranged between 150-200ng/ml, resulted in minimal toxic cyclosporine effects with less risk of opportunistic infections.

Besides, Iyer *et al.* (2014) correlated between intestinal infection (with parasites, cytomegalovirus, or *Clostridium difficile*) and clinical disease severity in patients with ulcerative colitis. Conner *et al.* (2019) in USA reported that in AIDS patients with chronic diarrhea, proper testing for both CMV and cryptosporidiosis *parvum* was vital.

Conclusion

The organ transplant recipients receive immunosuppressive regimens to avoid transplant rejection and thus at increased risk for opportunistic infections especially the cytomegalovirus.

The short-term outcomes on renal transplanted patients about incidence of CMV colitis, hepatitis and rejection rates between tacrolimus and cyclosporine didn't show significant difference between both groups.

Recommendation

Treatment of CMV isn't indicated for the healthy children and adults as well as mild cytomegalovirus infection. Even the healthy adults who developed CMV mononucleosis generally recover without medication.

However, the newborns and people with weak immunity are treated when they're experiencing symptoms of CMV infection. Besides, the mild CMV infection is usually not treated

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All authors equally shared in the study and critically revised the manuscript and approved its publication

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