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INCIDENCE OF CYTOMEGALOVIRUS DISEASE IN KIDNEY TRANSPLANT RECIPIENTS RECEIVING EVEROLIMUS AND REDUCED TACROLIMUS DOSES: A COHORT RETROSPECTIVE ANALYSIS

Incidência de Doença por Citomegalovirus em receptores de transplante renal recebendo Everolimus e dose reduzida de Tacrolimus: Análise de uma coorte retrospectiva

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RESUMO

Introduction: Cytomegalovirus (CMV) is the most common viral pathogen occurring in postrenal transplantation. CMV infection usually develops during the first few months after transplantation. The success of CMV prophylaxis with antivirals has resulted in a decrease in the incidence of CMV infection. However, CMV remains a significant pathogen, associated with allograft rejection and loss, mortality, interstitial fibrosis and tubular atrophy (IF/TA) in protocol biopsies, and increased post-transplant costs. **Purpose**: To determine the incidence of cytomegalovirus disease in kidney transplant recipients receiving Everolimus and reduced Tacrolimus doses. **Material and Methods**: All low immunological risk patients, >18 years old whom received kidney transplantation at Santa Casa de Misericórdia de Juiz de Fora between January 2013 and February 2017 were retrospectively assessed. The first group received induction therapy with Basiliximab, and the post-operative maintenance regimen included Tacrolimus, Mycophenolic acid and Prednisone (BAS/MPS), and the second group received Polyclonal antilymphocyte globulins (2,25mg/kg) as induction therapy, and then low dose of Tacrolimus (2mg/10kg/day), Everolimus and Prednisone as maintenance regimen (r-ATG/EVR). None of the patients received pharmacological prophylaxis or preemptive therapy against CMV. **Results**: Patients receiving EVR showed a lower incidence of CMV when compared to those receiving MPS (4.2% x 17.5%, p=0.005). There was an important difference in the time of hospitalization to treat CMV disease. Patients of the MPS stayed hospitalized for about 20 days more than the EVR group (p=0.005). There was no difference as to the incidence of rejection, delayed graft function or graft survival. **Conclusion**: Results from this trial conducted in low immunological risk kidney transplant recipients receiving no CMV prophylaxis demonstrated that EVR was associated to a decrease in CMV disease incidence when compared to MPS. These data suggest that kidney transplant recipients receiving EVR may not need CMV prophylaxis.

Keywords: Cytomegalovirus; Kidney Transplant; mTOR inhibitors

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INTRODUCTION

Cytomegalovirus (CMV) is the most common viral pathogen occurring in postrenal transplantation.[1-4] CMV infection usually develops along the first few post-transplantation months. The clinical picture of infection ranges from self-limiting asymptomatic viremia to CMV infection (fever, malaise, leukopenia), to life-threatening tissue-invasive disease (i.e., pneumonia, hepatitis, multiorgan failure).[5,6] The success of CMV prophylaxis with antivirals has resulted in a decrease in the incidence

of CMV infection1, [7-10] However, CMV remains a significant pathogen, associated with allograft rejection and loss, mortality, interstitial fibrosis and tubular atrophy (IF/TA) in protocol biopsies, and increased the post-transplant costs.[1,11-15]

The prevalence of CMV seropositivity varies around the world, ranging from 40% to 100%, with lower rates in Europe, North America, and Australia and with higher rates in Africa and Asia.[5,16] Recipients who are seronegative for CMV are at the greatest risk of disease after receiving allografts from infected, seropositive donors (donor positive/recipient negative combinations).[6,17] Without adequate preventive therapy to control viral replication, it is estimated that approximately 58% to 80% of solid organ transplant recipients develop active CMV disease.[17-19]

Universal prophylaxis and preemptive therapy have been used to manage CMV infection, but both are associated to disadvantages.[20-23] Pre-emptive therapy does not prevent viral replication, an event that has been associated to poorer transplant outcomes, and requires intensive logistical coordination.[20,21,23-26] Universal prophylaxis is not fully effective, and its duration of 3–6 months varies according to the perceived risk is associated to bone marrow adverse events, possibly leading to drug dose discontinuation.[20,27,28] and it is associated to a significant incidence of late CMV infection and drug resistance.[20,22,29,30] Ganciclovir and valganciclovir have become the antiviral agents of choice for prevention and treatment of CMV infection in these patients.[27,28,31] However, with the widespread use of these drugs, an increase in the incidence of ganciclovir-resistant (GanR) CMV strains has been reported.31. Among SOT recipients, GanR CMV infection may be associated with aggressive clinical courses, organ dysfunction, and mortality.[31,32] Moreover, GanR CMV poses particular management difficulties because foscarnet and cidofovir can be extremely toxic.[31,32] An effective immunosuppressive drug in preventing rejection that attenuated the incidence of CMV events would be beneficial to patients.[1]

In recent years, many observational studies showed that mammalian target of rapamycin inhibitors (mTORi) has a protective effect for CMV infection after solid organ transplantation, especially after KT.[1,5,17,33-40] CMV replication is dependent upon 1 of 2 mTOR pathways, and in vitro studies support an association between mTOR inhibitors and decreased CMV.[1,41] The risk to acquire CMV on an mTORi was lower than half when compared to patients on CNI. Corresponding to the ‘‘natural’’ peak of CMV infections after transplantation, the anti-CMV effect seemed most pronounced in the studies using de novo mTORi or very early conversion approaches.[5] Moreover, there is also some evidence on the efficacy of the conversion from calcineurin inhibitors (CNI) to mTORi to control the replication of ganciclovir-resistant CMV.[31,33,42]

MATERIALS AND METHODS

Population

This single-center retrospective cohort analysis aimed to assess the impact of the use of mTORi on the risk for CMV disease in low immunological risk patients of de novo kidney transplant receiving no pharmacological prophylaxis.

All low immunological risk patients, >18 years old whom received kidney transplantation at Santa Casa de Misericórdia de Juiz de Fora between January 2013 and February 2017 were retrospectively assessed. Patients were followed till 01/01/2018 or until they completed 1 post-transplantation year.

Patients were categorized according to the immunosuppression regimen, regardless the need for treatment discontinuation (intention-to-treat analysis).

Immunosuppression protocol

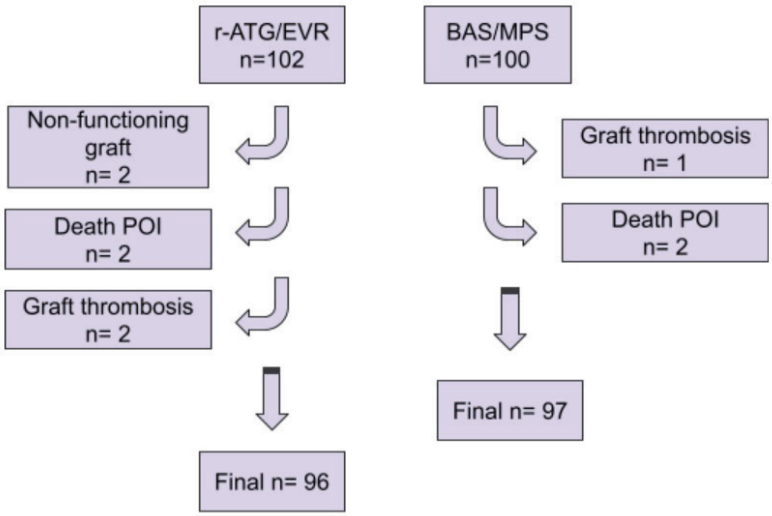
In 2013, all patients received induction therapy with Basiliximab, and the post-operative maintenance regimen included Tacrolimus, Mycophenolic acid and Prednisone (BAS/MPS). From January 2015 all patients received Polyclonal antilymphocyte globulins (2,25mg/kg) as induction therapy and then low dose of Tacrolimus (2mg/10kg/day), Everolimus and Prednisone as maintenance regimen (r-ATG/EVR). In 2014 there was a transition between the protocols when only recipients of living kidney donation were allocated in the r-ATG/EVE group. None of the patients received pharmacological prophylaxis or preemptive therapy against CMV.

Exclusion criteria included patients who lost graft within the first week of transplantation (Figure 1).

Definitions

We considered low immunological risk patients with panel reactive antibody (PRA) lower than 50% and without donor-specific antibodies (DSA). The diagnosis of CMV disease was made from the clinical suspicion, next confirmed by quantitative plasma PCR >1.000 copies/ml. Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation. Biopsy confirmed acute rejection episodes were classified according to Banff’s 2009 classification.[28]

***Figure 1** - Exclusion criteria*



CMV disease was defined as positive PCR and symptoms (fever; malaise or fatigue; leukopenia or neutropenia; atypical lymphocytosis; thrombocytopenia) or tissue-invasive disease.

This study was approved by the Santa Casa de Misericórdia de Juiz de Fora ethical committee on 04/11/2017 (Parecer Consubstanciado no. 2.011.836). The inform consent was exempted.

RESULTS

There were no significant differences between demographic characteristics of the recipients, except for the panel reactive antibodies class II, which was lower in the EVR group (**Table 1**). When analyzing the donor characteristics, we observed that the number of mismatches was higher in the MPS group; there were more living and male donors in the EVR group, and the cold ischemia type was higher in this group, as well. There was a significant difference in the combination of donor and recipient CMV IgG pre-transplantation serologic status, and therefore we analyzed separately the incidence of CMV disease in both positive and negative recipients.

Patients receiving EVR showed a lower incidence of CMV disease when compared to those receiving MPS (4.2% x 17.5%, p=0.005, **Figure 2**, **Table 2**).

***Figure 2** - CMV disease cumulative incidence*

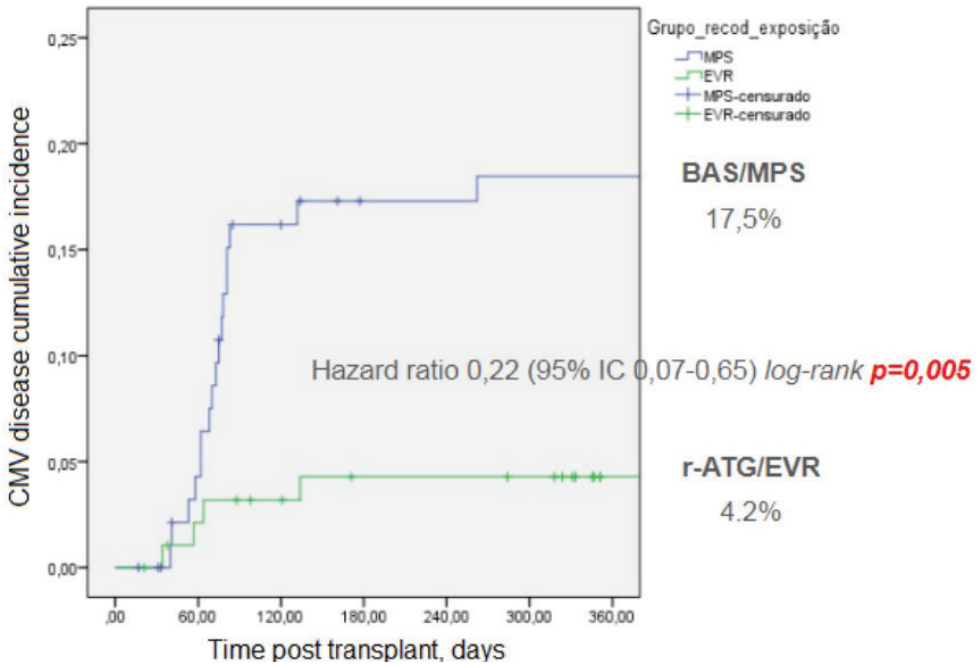


***Table 1** - Demographic characteristics*

Variable	r-ATG/EVR (N = 96)	BAS/MPS (N = 97)	P
Recipient age (mean ± SD)	46.2 ± 12.4	49.3 ± 12.5	0.087
Recipient gender, male, N (%)	64 (66.7)	71 (73.2)	0.323
Body mass index (Kg/m²), (mean ± SD)	25.0 ± 4.3	24.9 ± 4.2	0.886
Cause of chronic kidney disease, N (%)			0.146
Undetermined	36 (37.5)	28 (28.9)	
Hypertension	17 (17.7)	31 (32)	
Diabetes mellitus	14 (14.6)	(15.5)	
Polycystic disease	9 (9.4)	5 (5.2)	
Glomerulonephritis	9 (9.4)	11 (11.3)	
Urological disease	3 (3.1)	0	
Other	8 (8.3)	7 (7.2)	
Time on dialysis, months (mean ± SD)	35.1 ± 36.9	37.3 ± 40.2	0.330
Type of treatment, N (%)			0.42
Hemodialysis	89 (92.7)	93 (95.9)	
Peritoneal dialysis	4 (4.2)	3 (3.1)	
Preemptive transplantation	3 (3.1)	1 (1)	
Panel reactive antibodies, (%)			
Class I (mean ± SD)	4.0 ± 10.9	2.7 ± 5.6	0.088
Class II (mean ± SD)	0.4 ± 3.3	3.6 ± 11.1	0.002
HLA mismatches (mean ± SD)	3.7 ± 1.3	4.3 ± 1.3	0.001
CMV IgG serologic status, N (%)			0.000
Donor (+)/Recipient (+)	70 (72.9)	42 (43.3)	
Donor (+)/Recipient (-)	1 (1)	4 (4.1)	
Donor (-)/Recipient (+)	17 (17.7)	15 (15.5)	
Donor (-)/Recipient (-)	1 (1)	1 (1)	
Donor (unk)/Recipient (-)	0	2 (2,1)	
Donor (unk)/Recipient (+)	7 (7.3)	33 (34)	
Retransplantation	0	0	
Donor age, years (mean ± SD)	43.5 ± 10,9	43.6 ± 13.8	0.958
Donor gender, male, N (%)	60 (62.5)	47 (48.5)	0.050
Donor type, N (%)			0.005
Living	41 (42.7)	23 (23.7)	
Deceased	55 (57.3)	74 (76.3)	
Cause of donor death, N (%)			0.947
Cerebrovascular	34 (61.8)	49 (66.2)	
Head trauma	16 (29.1)	20 (27)	
Tumor	2 (3.6)	2 (2.7)	
Other	3 (5.5)	3 (4.1)	
Final donor creatinine, mg/dL (mean ± SD)	1.8 ± 1.3	1.7 ± 0.9	0.548
Cold ischemia time, hours (mean ± SD)	17.4 ± 6.3	14.8 ± 5.8	0.030

SD = Standard deviation

***Table 2** - Incidence of CMV disease*

Variable	r-ATG/EVR (N = 96)	BAS/MPS (N = 97)	P
Incidence of first CMV event, N (%)	4 (4.2)	17 (17.5)	0.005
Time to first CMV event, days (mean ± SD)	72.2 ± 43.1	82.1 ± 50.7	0.420
PCR, copies/mL (mean ± SD)	222.823,7 263.235,3	± 200.472,9 376.392,4	0.362
Duration of hospitalization treatment, days (mean ± SD)	11.7 ± 13.6	32.9 ± 8.8	0.005
Pretransplant CMV serostatus, N (%)	-	-	-
Donor (+)/Recipient (+)	2 (2.9)	6 (14.3)	0.051
Donor (+)/Recipient (-)	1 (100)	2 (50)	1.000
Donor (-)/Recipient (+)	0	0	-
Donor (-)/Recipient (-)	1 (100)	0	-
Donor (unk)/Recipient (-)	0	1 (50)	-
Donor (unk)/Recipient (+)	0	8 (24.2)	-
Recipient (+)	2 (2.1)	14 (15.6)	0.001
First CMV event after EVR discontinuation, N(%)	0	-	-

SD= Standard deviation

When we analyzed the recipients who were previously positive for CMV IgG, and we observed a statistically significant difference (2.1% x 15.6%, p=0,001), that was not observed in the negative CMV IgG recipients, probably due to the small sample. There was an important difference in the time of hospitalization to treat the CMV disease; patients of MPS stayed hospitalized for about 20 days longer than the EVR group (p=0.005), including 2 patients that did not need to be admitted for treatment.

DISCUSSION

Tedesco-Silva et al. assessed a group of de novo kidney transplant recipients treated with a single dose of antithymocyte globulin (ATG) and a reduced dose of tacrolimus and everolimus without CMV prophylaxis. A significant reduction in the incidence of CMV infection/disease was observed in comparison to the standard tacrolimus plus mycophenolate immunosuppressive regimen.[20,33]

In a pooled analysis of over 2000 de novo RTX recipients in 2011, Brennan, et al. demonstrated that EVR was associated to a decrease and delay in the time to onset of CMV events compared to MPA.[1]

CMV infection is associated to many deleterious indirect effects including rejection,[1,11] IF/TA[1,15] and mortality1,[11-13] In addition to the potential for undesirable clinical outcomes associated to the CMV, there is also a negative economic aspect. Perhaps most costly, it is the economic burden of CMV-associated graft failure.[1,43]

The use of an mTOR inhibitor as part of the immunosuppressive regimen could also be considered in recipients with CMV disease resistant to antiviral therapy. In a study of nine renal transplant recipients who had ganciclovir-resistant CMV,[42] a rapid decrease in antigenemia levels was observed after conversion to sirolimus and ganciclovir administration, and none of the recipients experienced acute rejection or CMV recurrence.[17]

***Table 3** - Secondary endpoints*

Variable	r-ATG/EVR (N= 96)	BAS/MPS (N= 97)	P
Treatment failure, N (%)	16 (16.7)	6 (6.2)	0.025
First biopsy confirmed acute rejection, N (%)	4 (4.2)	6 (6.2)	0.747
IA	0	1 (16.7)	-
IB	0	1 (16.7)	-
IIA	1 (25)	3 (50)	-
IIB	1 (25)	0	-
III	0	1 (16.7)	-
Mixed	1 (25)	0	-
Acute antibody-mediated rejection	1 (25)	0	-
Patient survival, 12 months, (%)	89.5	85.6	0.449
Graft survival, 12 months, (%)	88.5	80.4	0.102
Death-censored graft survival, 12 months (%)	98.9	94.5	0.079
DGF, N (%)	20 (36.4)	37 (50)	0.123
Duration of DGF, days (mean ± SD)	7.6 ± 6.2	10.7 ± 10.9	0.570
Creatinine, mg/dL (mean ± SD)			
3 months	1.9 ± 1.0	2.0 ± 0.9	0.175
6 months	1.8 ± 0.9	2.0 ± 0.8	0.111
12 months	1.9 ± 1.0	1.9 ± 1.2	0.67

SD - Standard deviation

The association of lower CMV with the use of EVR might be explained by relatively less potent immunosuppression. However, the acute rejection rates were similar between those who received EVR compared to MPA, suggesting that the "net state of immunosuppression" for any group was similar.[1,2]

A higher number of patients in the EVR group needed discontinuation of the therapy (p= 0.025, Table 3), maybe because we use adjustment of dose for patients receiving MPS before discontinuation, and because of the lack of experience with the new drug at this point. These findings are consistent with the literature.[44,45] There were no differences in DGF, graft or patient survival, acute rejection or creatinine levels.

Despite being a single-center retrospective study, the present analysis corroborates previous findings.[20,33]

CONCLUSION

Results from this trial conducted in low immunological risk kidney transplants recipients receiving no CMV prophylaxis or preemptive therapy demonstrated that EVR was associated to a decrease in CMV disease incidence when compared to MPS. Except for the underrepresented high-risk population (D+/R-), these data suggest that kidney transplant recipients receiving EVR may not need CMV prophylaxis.

RESUMO

Introdução: Citomegalovírus (CMV) é a infecção viral mais comum após o transplante renal. CMV. Geralmente apresenta-se nos primeiros meses após o transplante. O uso de terapia profilática com antivirais resultou em queda da incidência, porém, CMV ainda permanece como uma comorbidade importante, associada com rejeição e perda do enxerto, mortalidade, fibrose intersticial e atrofia tubular (IF/TA) em biópsias protocolares e aumento de custo. **Objetivo**: Determinar a incidência de doença pelo citomegalovírus em receptores de transplante renal recebendo Everolimus e dose reduzida de Tacrolimus. **Materiais e Métodos**: Foi realizada análise retrospectiva envolvendo pacientes de baixo risco imunológico que receberam transplante renal na Santa Casa de Misericórdia de Juiz de Fora, entre Janeiro de 2013 e Fevereiro de 2017. O primeiro grupo recebeu indução com Basiliximab e terapia de manutenção pós-operatória com Tacrolimus, Ácido micofenólico e Prednisona (BAS/MPS) e o segundo grupo foi induzido com Globulina anti-linfócito (2,25mg/Kg) e regime de manutenção com Tacrolimus em baixa dose (2mg/10Kg/dia), Everolimus e Prednisona (r-ATG/EVR). Nenhum paciente realizou terapia preemptiva ou profilaxia contra CMV. **Resultados**: Pacientes que receberam EVR apresentaram menor incidência comparados aos que receberam MPS (4.2% x 17.5%, p=0.005). Houve importante diferença no tempo de hospitalização para tratamento de CMV; aqueles recebendo MPS permaneceram internados cerca de 20 dias mais do que o grupo EVR (p=0.005). Não foram observadas diferenças na incidência de rejeição, função retardada do enxerto ou sobrevida do enxerto. **Conclusão**: Resultados deste trabalho conduzido em receptores de transplante renal de baixo risco imunológico que não receberam profilaxia contra CMV demonstram que EVR está associado à menor incidência de doença por CMV, quando comparado à MPS. Esses dados sugerem que receptores de transplante renal recebendo EVR podem não usar profilaxia contra CMV.

Descritores: Citomegalovírus; Transplante renal; inibidores da mTOR.

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