Considering Prophylaxis for Cytomegalovirus Disease in Cytomegalovirus Positive Renal Transplant Recipients from Positive Donors in a Resource Limited South African Public Hospital

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Abstract

Giving cytomegalovirus (CMV) prophylaxis to CMV positive recipients is expensive in a resource-limited setting like South Africa. We report a retrospective analysis of CMV disease in 47 CMV donor/recipient positive (D+/R+) adult renal transplant patients (> 80% African Blacks) from February 2000 to November 2004 who had received four drug induction immune suppression. We commenced routine valganciclovir prophylaxis for 3 months post renal transplant in January 2007 and reviewed incidence of CMV disease from January 2007, in similar patients, until October 2009. Before prophylaxis, incidence of CMV disease was 32% in D+/R+ and was similar to recipient negative/donor positive (D-/R+) patients, however graft survival analysis adjusted for CMV disease showed that D+/R+ recipients had a hazard ratio of 2.8 (p=0.03) for poor graft outcome. After prophylaxis, among deceased donor recipients the incidence of CMV disease over a mean follow up of 17.3 months was 6% (n=2), and nil in live donor recipients. Our immunosuppressive therapy carries a risk of CMV disease in approximately a third of patients and is associated with poorer graft outcomes. CMV prophylaxis has been highly effective at reducing the incidence of CMV disease, and is important in a setting with ever decreasing availability of organs for transplantation.

Keywords: Cytomegalovirus; Infectious complications; Prophylaxis; Renal transplant

Abbreviations: CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; D+: Donor CMV IgG positive; R+: Recipient CMV IgG positive; D-Donor: CMV IgG negative; R-Recipient: CMV IgG negative; OKT3: Anti cluster of differentiation 3 antibody

Introduction

Cytomegalovirus is a very important infection in transplantation. Exposure to the virus, as detected by the presence of IgG anti-CMV antibodies in the plasma, is present in more than two thirds of donors and recipients prior to transplantation [1]. Thus it is common for both recipient and donor to be CMV-positive at the time of transplantation. Interestingly, most reports have inferred that the incidence of CMV infection due to blood transfusions in the renal transplant setting is probably low [2]. This may reflect the fact that renal transplant patients generally do not receive large volumes of transfused blood currently. It is established in renal transplantation that all renal parenchymal cells can be sites of viral latency and that reactivation of latent virus results in infection in the recipient [3]. Individuals may activate their own latent virus coincident with immune suppression. Chou [4] did however show that seropositive individuals can be re-infected by a new CMV strain from the donor after transplantation [4].

An important "co-factor" in reactivation of the virus from latency is tumour necrosis factor (TNF), which binds to a receptor on infected cells with signaling via protein kinase C and nuclear factor kappa B (NFKB). This leads to the formation of a viral protein p65/p50 NFkB hetero dimer, which translocates to the nucleus and binds to the CMV immediate early enhancer region, which induces viral replication. This is then followed by amplification and dissemination. This would help explain certain clinical observations, such as the fact that CMV infection and disease have been linked to allograft rejection, sepsis and the administration of anti-lymphocyte products, all which induce release of TNF [5-8]. Thus, the pro-inflammatory milieu seems to play an important role in viral reactivation.

In a South African setting, and particularly at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a public hospital, most transplants take place in patients at higher risk of rejection (black patients, poor HLA matching) [9]. This necessitates the use of potent immnosuppressive regimens, with significant morbidity from opportunistic infections. One of the most important of these is CMV disease. Within our own transplant unit, it had been noted recently that CMV disease is on the increase, adding significantly to the morbidity and costs associated with renal transplantation (unpublished observations). Hence it is an important problem that needs to be looked at.

The risk of infection/disease is dependent on the CMV antibody status of the donor and recipient. The highest risk group is that in which the recipient is CMV-negative and the donor is CMV-positive. Risk of primary infection is 70 to 90% with an incidence of disease of 50 to 80% with a 15% mortality rate [10]. Importantly, CMV infection may occur in 20% of CMV positive recipients from CMV negative donors [10]. In this situation the source of the CMV is not exactly clear, although blood products may play a role. CMV disease is typically not severe with D-/R+ transplants. With both donor and recipient CMV positivity, disease rates of up to 59% with Anti cluster of differentiation 3 antibody (OKT3) induction have been cited, whereas rates of around 21% are quoted in recipients not treated with OKT3 [11]. Cases with both donor and recipient negative for CMV have a very low prevalence of CMV infection. Concern naturally has focused mainly on the group at highest risk of infection and subsequent development of what is

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often severe disease, namely the CMV positive donor (D+) to CMV negative recipient (R-) transplants [12]. It has however, been noted that, at 3 years after transplantation, it may well be CMV D+/R+ transplants that have a worse outcome [13]. This may be due to the presence of multiple CMV genotypes from varied donor and recipient CMV strains [13]. Similarly, Manuel et al showed that showed that in seropositive recipients, transmission or reactivation of multiple CMV strains is possible, based on genotyping [14].

Therapy for graft rejection usually comprises high dose steroids and occasionally even polyclonal immune globulins, which also places patients at higher risk of opportunistic infections. It has also been noted that blood transfusions, particularly from CMV positive donors (a large proportion of the population) also contribute to risk of CMV disease post transplantation [15]. There is a wide range of reported incidence of CMV infection and disease which largely reflects the intensity of immunosuppressive regimens used. It is known that the use of antithymocyte globulin (ATG), and other polyclonal immune globulins, significantly reduces the risk of rejection at the expense of significant increase in the incidence of CMV disease – up to 43% in one study [16]. The Anti-IL-2 (Interleukin 2) receptor antibodies (Daclizumab and Basiliximab) have been thought to be at least part of the solution to one of the most difficult problems in transplantation, namely balancing the amount of immunosuppressive therapy to minimise both risk of rejection and opportunistic infections or malignancies. It would appear, from several international studies, that the use of Anti-IL-2 receptor antibodies has achieved this goal with reports of minimal rejection and decreased incidence of CMV disease [17-20].

The CMJAH transplant unit has been using these and other potent agents like mycophenolate mofetil (MMF) since February 2000. The impact of MMF on the incidence and effect of CMV disease on patient and graft survival is also controversial. Data suggests that MMF is associated with a higher or similar incidence of CMV disease [21-23] (certainly in D+/R- transplants) and may be associated with more organ involvement [21], however, overall graft survival is still better than with the previously used antimetabolite, azathioprine [24,25].

At the CMJAH anti-IL-2 receptor antibodies are incorporated into 4 drug induction regimens, as most of our transplant recipients are at high risk of rejection, being largely black Africans and poorly HLA matched. It is accepted that CMV D+/R- transplants require prophylaxis and there is some debate in the literature as to which is the optimal prophylactic regimen, i.e., intravenous ganciclovir, oral ganciclovir, oral valganciclovir, oral acyclovir, CMV hyperimmune globulin and various combinations of these [26-29]. Ganciclovir needs to be triple phosphorylated by a CMV hyperimmune globulin and various combinations of these products) [35]. In January 2007, having noted high numbers of admissions for CMV disease, we began using routine prophylaxis with valganciclovir for the first three months post renal transplant to try and reduce incidence of CMV disease in our patients.

Methods and Materials

Approval for this work was obtained from the ethics committee of the University of the Witwatersrand, approval number M020453.

Prior to prophylaxis

We reviewed patients who had received MMF, Basiliximab, CyA and corticosteroids between 2000 and November 2004. A total of 73 adult transplant recipients were considered for review based on the above criteria. Further selection involved a review of the transplant registry for CMJAH to confirm donor and recipient CMV serological status. Twenty two of the above recipients were found to have received allografts from CMV seronegative donors at the time of transplantation and their data was separated from the D+/R+ group. It was considered that their data would make a useful outcome and incidence control group. CMV status was not checked in the donor at the time of transplantation in one of the CMV positive recipients, and thus the recipient was excluded from further analysis. Of the CMV D+/R+ group, 3 of the recipients had follow up times of 1 month or less due to early graft loss - 1 demised at 1 month from sepsis, 1 was nephrectomized at 1 month for sepsis and the remaining patient had primary non-function as was found to have cortical necrosis at nephrectomy. As it is unlikely that they would have had CMV disease so soon after transplantation, they were excluded from analysis. This left 47 patients for analysis in the D+/R+ group, 22 patients’ data was available for comparison in the D+/R+ group.

The CMJAH anti-IL-2 receptor antibodies are incorporated into 4 drug induction regimens, as most of our transplant recipients are at high risk of rejection, being largely black Africans and poorly HLA matched. It is accepted that CMV D+/R- transplants require prophylaxis and there is some debate in the literature as to which is the optimal prophylactic regimen, i.e., intravenous ganciclovir, oral ganciclovir, oral valganciclovir, oral acyclovir, CMV hyperimmune globulin and various combinations of these [26-29]. Ganciclovir needs to be triple phosphorylated by a CMV UL97 gene encoded phosphotransferase and cellular kinases to the active triple phosphate form which inhibits the CMV UL54 gene encoded DNA polymerase which is responsible for DNA synthesis [30]. Valganciclovir is a valyl ester of ganciclovir which increases the oral bioavailability of the drug by 10 fold, while ganciclovir is poorly absorbed orally [31]. CMV infected cells are unable to phosphorylate acyclovir and valacyclovir and pharmacologically speaking, these drugs should have no activity against CMV. Published studies have shown them to be somewhat effective as prophylaxis, although how this occurs remains to be explained [32]. Recently a study from Ireland has shown that acyclovir prophylaxis did not improve renal allograft outcomes [33]. There have also been published reports of acute renal failure and neurotoxicity using these agents, particularly in those with renal dysfunction (like new transplants), making the use of these agents as prophylaxis challenging [34]. All of these agents tend to be expensive to use for prophylaxis, which is a problem in a public hospital such as CMJAH where resources are constrained.

As such, CMV D+/R+ transplants were not routinely given CMV prophylaxis and a “wait and see” attitude was adopted. This appeared to be in line with accepted clinical practice guidelines, which on the basis of Grade A levels of evidence, recommend antiviral prophylaxis only in those patients who are D+/R+ who have received antilymphocyte products [10]. The use of prophylaxis in this group of patients would be supported by Grade C levels of evidence and left to the discrimination of the physician treating these patients [9]. Recently the consensus guidelines have suggested that R+ patients should receive 3 months of drug prophylaxis (or 3 to 6 months for those receiving antilymphocyte products) [35]. In January 2007, having noted high numbers of admissions for CMV disease, we began using routine prophylaxis with valganciclovir for the first three months post renal transplant to try and reduce incidence of CMV disease in our patients.

Episodes of rejection and associated high dose SoluMedrol administration were recorded; in addition a temporal relationship with onset of CMV disease post high dose steroid was investigated. As a marker of overall immune suppression, time to a low dose range of steroid (7.5 mg per day of prednisone) was also recorded. All eligible patients had received the same dose of Basiliximab at induction, i.e., 20 mg intravenously on day 0 and day 4 post transplantation. Cyclosporine was given according to standardized blood levels (both trough and two hour post dose levels were used) and all patients were given MMF at 1g twice daily unless they had gastrointestinal side effects.

Blood transfusion prior to onset of CMV disease was also recorded. Presenting clinical features of CMV disease were recorded, as well as the method used to diagnose CMV disease was recorded. At the CMJAH transplant unit, the diagnosis of CMV disease is suspected in patients with a combination of clinical features, particularly unexplained fever, leucopenia and graft dysfunction, and confirmed with laboratory tests.

At the time of the initial analysis, qualitative pp65 antigenemia
positiveity (in the absence of severe leucopaenia) was used in diagnosing CMV disease. No patient was included in the analysis if CMV was “diagnosed” purely on clinical suspicion.

Patient and graft survival were recorded. Graft outcome was defined as “good” if serum creatinine was less than 200 µmol/l, “poor” if serum creatinine was more than 200 µmol/l and “loss” if the patient returned to dialysis. Death with a functioning graft was also recorded. Recurrence of CMV disease was also noted.

The Stata statistical programme was used for analysis. Outcome variables were largely categorical for the purposes of this study and the numbers of patients reviewed was relatively small, thus Fisher’s exact test was used to assess significance between variables. Survival analysis and hazard ratios were derived using Cox proportional regression. A p value < 0.05 was defined as being statistically significant.

After prophylaxis

Prophylaxis was commenced on all recipients except those known to be D-/R-, in January 2007, with valganciclovir 450 mg twice daily if renal function was normal or once daily if renal function was abnormal. The files of 70 transplant recipients given sequential induction therapy from that date to December 2009 were reviewed (55 deceased donor recipients and 15 live donor recipients). Demographic data was recorded, CMV serology data was collected from the unit registry and outcome data in terms of serum creatinine and occurrence of CMV disease. No patient was included in the analysis if CMV was diagnosed on renal allograft biopsy by histological features of typical tubular viral inclusions in 1 patient from each group. All other patients were diagnosed with CMV disease based on pp65 antigenaemia. Importantly pp65 in our setting is a qualitative test only, i.e., not expressed as number of leucocytes showing antigen positivity. Mean onset to CMV disease was 4.78 months post transplant (range 2-24 months [in only 1 patient was onset >5 months]).

Patients’ renal function was expressed as serum creatinine as a measure of glomerular filtration rate (eGFR) formulae in published literature, as it seems that the effects of steroids on muscle mass significantly interfere with the accuracy of eGFR formulae [36]. The data of 44 patients was ultimately analyzed and the reasons for exclusion of the other 26 patients’ data being excluded are summarized in (Table 1).

Results

Demographic data for the patient groups before and after prophylaxis are summarized in (Table 1).

There are no statistically significant differences between the two groups of patients.

<table>
<thead>
<tr>
<th></th>
<th>D+R+ group (before prophylaxis)</th>
<th>D-/R+ group (before prophylaxis)</th>
<th>D+R+ (after prophylaxis)</th>
<th>Others (D-/R+, D-/R-) (after prophylaxis)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>47</td>
<td>22</td>
<td>36</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Male: Female</td>
<td>2.92:1</td>
<td>2.66:1</td>
<td>2:1</td>
<td>1:1</td>
<td>NS</td>
</tr>
<tr>
<td>Number of Black patients</td>
<td>38 (80.9% Black)</td>
<td>20 (90.9% Black)</td>
<td>28 (78% Black)</td>
<td>5 (63% Black)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean±SD age (years)</td>
<td>41 ± 11.2</td>
<td>37.7 ± 9.4</td>
<td>40.64 ± (10.49)</td>
<td>40.63 ± (14.73)</td>
<td></td>
</tr>
<tr>
<td>Mean±SD follow up (months)</td>
<td>25.6 ± (14.3)</td>
<td>32 ± (14.2)</td>
<td>17.18 ± (10.25)</td>
<td>20.13 ± (11.75)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>5 (10.6%)</td>
<td>1 (4.6 %)</td>
<td>0 (0%)</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
</tbody>
</table>

* T-test used to compare means. Otherwise Fisher’s exact test used to compare categorical variables.

Table 1: Demographic data of the D+/R+ group and D-/R+ group before CMV prophylaxis.

Prior to prophylaxis

Of the 5 patients in the D+/R+ group who died, 2 had well functioning grafts and died of intra cerebral haemorrhage and cerebral venous sinus thrombosis. The remaining 3 patients who died had graft loss and died of HIV related complications (Kaposi’s sarcoma), overwhelming sepsis and pulmonary embolism, respectively. In only one of the patients was CMV diagnosed and was unlikely to be related to death as CMV disease occurred 16 months prior to death. In the D-/R+ group, death was associated with graft loss and sepsis in the 1 patient who demised.

In the D+/R+ group, 15 (32%) of the patients developed a total of 17 episodes of CMV disease (2 with recurrent CMV disease). Incidence of CMV disease (6 patients [27.27%]) in the D-/R+ group was not significantly different from the D+/R+ group (p=0.78). One patient in the D-/R+ group had recurrent disease. The incidence of recurrent disease between the D+/R+ and D-/R+ groups was also not significant (p=1.000).

CMV was diagnosed on renal allograft biopsy by histological features of typical tubular viral inclusions in 1 patient from each of the D+/R+ and D-/R+ groups. All other patients were diagnosed with CMV disease based on pp65 antigenaemia. Importantly pp65 in our setting is a qualitative test only, i.e., not expressed as number of leucocytes showing antigen positivity. Mean onset to CMV disease was 4.78 months post transplant (range 2-24 months [in only 1 patient was onset >5 months]).

Mean onset to CMV disease for the D+/R+ group was 4.78 months post transplant (range 2-24 months [in only 1 patient was onset >5 months]).

Mean onset to CMV disease for the D+/R+ group was 10 months (range 3-28 months [in 3 patients onset was >5 months]). (Table 2) outlines categorical variables that were looked at specifically in the D+/R+ group that may predict occurrence of CMV disease, and the same factors were analyzed in the D-/R+ group with very similar results (none significant). Cox regression to analyze the impact of the above factors and continuous variables (specifically dose of prednisone and age) was able to identify two variables as important predictors of CMV disease (Table 3) - higher doses of prednisone and older age (with incremental increase in risk for each decade). The same factors for the D+/R+ group were not predictive of CMV disease in the D-/R+ group although this was a smaller group of patients.

Figure 1: Patient file data and reasons for exclusion (post prophylaxis analysis).

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In the D+/R+ transplant recipients, leucopaenia and graft dysfunction were highly statistically significant clinical findings in those with CMV disease (p=0.000 and p=0.000 respectively).

Importantly there was a highly statistically significant association in the D+/R+ group with CMV disease and concomitant sepsis (p=0.000). The sepsis occurred predominantly in the form of urinary tract infection. 83% of episodes of concomitant sepsis were urinary tract infections with urine culture positive in all but 1. The remaining episode of sepsis was pneumonia with stenotrophomonas isolated on blood culture.

When the D+/R+ and D-/R+ groups are compared, overall patient survival over the months of follow up is similar (Table 1).

For the purposes of survival analysis, both poor graft function and graft loss were defined as "bad" graft outcome. Cox proportional regression adjusted for CMV, time to reduce prednisone dose to 7.5 mg per day, age and D+/R+ vs. D-/R+ groups shows that the D+/R+ group has a hazard ratio for bad graft outcome of 2.8, which was significant (Figure 2).

After prophylaxis

The demographic characteristics of the group of patients analyzed after institution of prophylaxis, as well as renal function at end of follow up, are shown in (Table 1). It should be noted that the demographic data of patients before and after prophylaxis remained similar. The impact of prophylaxis in terms of reducing the incidence of CMV disease in all groups and particularly the D+/R+ was quite remarkable (Figure 2).

Graft outcomes for the groups analysed before and after prophylaxis are shown in (Table 4). Chi square analysis of good outcome vs. loss in D+/R+ group before vs. D+/R+ group after prophylaxis was significant with p = 0.0324, but one must take in to consideration the disparate mean follow up times.

Discussion

As would be reflective of the typical demographic distribution of ethnicity in South Africa, the vast majority of patients transplanted at the CMJAH (as reviewed in this study) are Black Africans. As such, these patients represent a unique challenge for transplant physicians. Not only are they more prone to rejection as highlighted in the introduction, but their poorer socio-economic circumstances predispose them to acquiring more CMV infection pre-transplant, and hence likely more re-activation of disease post transplantation, in part related to four drug induction immunosuppression, and three drug maintenance immunosuppression. One of the challenges facing a transplant physician would be to minimize rejection episodes while at the same time minimizing opportunistic infections.

It should be noted that the mean ages of the transplanted patients in this study is around 40 years. This is significantly younger than in the developed world. This partly reflects the selection criteria for the state funded dialysis and transplant programme in South Africa, in which patients over the age of 60 years are generally excluded.

Table 1: Categorical variables that may predict CMV disease (D+/R+ group) before prophylaxis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency in patients who developed CMV disease</th>
<th>Frequency in patients who never developed CMV disease</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M vs. F)</td>
<td>12 (80 %) vs. 3 (20 %)</td>
<td>23 (71.88%) vs 9 (28.13%)</td>
<td>0.725</td>
</tr>
<tr>
<td>Ethnic group (Black vs. Non Black)</td>
<td>14 (93.33%) vs. 1 (6.67%)</td>
<td>24 (75%) vs. 8 (25%)</td>
<td>0.236</td>
</tr>
<tr>
<td>Donor type (Live vs. Cadaver)</td>
<td>0 (0%) vs. 15 (100%)</td>
<td>5 (15.63%) vs. 27 (84.38%)</td>
<td>0.162</td>
</tr>
<tr>
<td>Transfusion before onset of CMV disease (Yes vs. No)</td>
<td>3 (20%) vs. 12 (80%)</td>
<td>0 (0%) vs. 32 (100%)</td>
<td>0.028 *</td>
</tr>
<tr>
<td>Acute rejection before onset of CMV disease (Yes vs. No)**</td>
<td>6 (40%) vs. 9 (60%)</td>
<td>14 (43.75%) vs. 18 (56.25%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Therapy for Rejection before onset of CMV disease (Yes vs. No)**</td>
<td>6 (40%) vs. 9 (60%)</td>
<td>12 (37.5%) vs. 20 (62.50%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Although transfusion appeared to be a significant risk factor based on univariate analysis, it emerged as a significant confounder in the regression analysis, perhaps related to small and very disparate numbers of patients.

**Biopsy proven rejection rates overall in the D+/R+ group vs. the D-/R+ group were 36.2% and 31.8% respectively (p=0.79 Fisher’s exact test). In each group rejection was diagnosed and treated empirically in 0.06% and 0.09% of the overall patients respectively, with 85% and 77.8% of acute rejections proven on histology. As can be seen from the table, there was no temporal relationship between rejection, or therapy for rejection, and occurrence of CMV disease.

Table 2: Categorical variables that may predict CMV disease (D+/R+ group) before prophylaxis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency in patients who developed CMV disease</th>
<th>Frequency in patients who never developed CMV disease</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3 month delay in reducing prednisone dose to 7.5 mg per day</td>
<td>1.209601</td>
<td>0.041</td>
<td>1.008124 - 1.494903</td>
</tr>
<tr>
<td>Increase in age every 10 years above age 18</td>
<td>2.10292</td>
<td>0.016</td>
<td>1.146961 - 3.855642</td>
</tr>
</tbody>
</table>

Table 3: Cox regression analysis for D+/R+ group – predictors of CMV disease D+/R+ group (before prophylaxis).
The overall patient survival in the two groups studied was 90-95% over an average follow up of 25 to 32 months. This probably reflects the fact that patients in South Africa are pre-selected and are likely to be healthier and younger. No patient died as a result of CMV disease as they were all treated with intravenous Ganciclovir, with primary CMV resistance to the drug being virtually non-existent [30]. It is difficult to use the term “incidence” strictly when discussing CMV disease, as risk is not equally distributed over a 12 month interval. As this study also clearly demonstrates, the vast majority of episodes of CMV disease will occur within the first 5 months of transplantation when immunosuppressive doses are at their highest. The incidence of CMV would largely depend on prevalence of CMV infection in the population and overall intensity of immunosuppression. To this end, it is difficult to find comparative literature upon which to judge our transplant unit, i.e., high intensity immunosuppression in a largely third world population. It would seem that average rates of CMV disease in D+/R+ transplants are 21% in the developed world. Perhaps the most direct form of comparison in terms of incidence of CMV disease would be to compare data presented at the launch of Basiliximab by Prof. J.R Botha in 2000 (unpublished) with previously used immunosuppressive regimens in our transplant unit. The use of azathioprine (AZA)/cyclosporine (CSA) and Prednisone induction alone was associated with rejection rates of 50% (n = 34 patients) and rates of CMV disease of 12% (n=34 patients). The addition of anti-thymocyte globulin for induction to the above regimen reduced rejection rates to 30% (n = 30), but was associated with rates of CMV disease of 33% (n = 30 patients). The data is however not censored for donor/recipient serological CMV status and rejection was often treated empirically on clinical suspicion.

As shown in the current study, the rates of CMV disease without prophylaxis in D+/R+ transplants in the CMJAH transplant unit are 32% over the follow up period, which is substantially higher than in more developed world centers. CMV disease in renal transplantation is an issue that very aptly demonstrates the interplay between economics and efficacy that tends to characterize modern medicine.

With this in mind, variables were reviewed that may predict or increase the risk of CMV disease that might be more easily modified so as to limit the necessity for prophylaxis. Probably the most important and obvious is the degree of immunosuppression to which the patient is exposed. Essentially it is the dose of steroid that is potentially the most modifiable and the most dependent on the involved transplant physician actively weaning the amount given. Along with the many known side effects of long term steroid use, exposure to steroid correlates with the degree of immunosuppression. It is not surprising then that this study shows a significant association between delay in steroid reduction and risk of CMV disease.

As previously mentioned, prevalence of CMV infection mirrors age. This study shows an association with advancing age and risk of CMV disease in this group of transplant patients. This has not previously been noted in literature, and was highly significant in this study. It has been noted that age related immune senescence may be induced by the impact of CMV infection on the accumulation of late differentiated CD8+ T cells which interfere with good proliferative responses, and predispose to other infections. What is not clear/published is whether this translates to increased risk of CMV disease in older transplant recipients [37]. This has important implications for considerations for prophylaxis, and perhaps a strong case could be made for the especially older D+/R+ recipients to be given prophylaxis. It would have been anticipated that black patients might be more at risk of CMV disease as they have poorer socioeconomic circumstances and are at greater risk for acute rejection and therefore tend to receive more overall immunosuppression than non-blacks, but this turned out not to be the case. What may have influenced statistical significance is the disparity in numbers of blacks vs. non-blacks. With the majority of transplant patients being black in this study, it is more difficult to compare the groups.

CMV prophylaxis dramatically reduced the incidence of CMV disease in our unit (6% in D+/R+ and nil in other serological groups) and this was highly statistically significant. It is difficult to comment on the impact of prophylaxis on graft outcomes as the follow up times in the pre and post prophylaxis groups are disparate at this early stage. What is more difficult to judge is whether prophylaxis in our developing country will be cost effective. Published literature is controversial in terms of D+/R+ transplants, and as such “the best approach to control of CMV after solid organ transplantation remains institution and resource dependent” [38]. In South Africa there are no data as to the costs of public hospital admissions per day. However one must balance the costs of prophylaxis versus the costs of the average 21 day admission required for IVI Ganciclovir administration, with consideration of the costs of treating concomitant sepsis as shown in this study, as well as the potential negative socioeconomic impact for our patients who live in a country where employment is difficult to find and sustain. Importantly, this study also demonstrates the negative impact CMV disease has on graft survival, and one must also take in to consideration the costs of returning to dialysis, both to the patient and the country as a whole.

The authors acknowledge that this data is retrospective and single centre and therefore open to selection bias. Despite this, it is apparent that CMV prophylaxis in our largely black and largely D+/R+ recipient population at high immunological risk has had a dramatic impact on reducing incidence of CMV disease.

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