The Effect of Gancyclovir Prophylaxis and Serological Matching on Symptomatic Cytomegalovirus Infection and Acute Rejection in Renal Transplant Recipients

By

Micah L. Thorp

A Dissertation

Presented to the Department of Public Health

and the Oregon Health Sciences University

School of Medicine

in partial fulfillment of

the requirements for the degree of

Master of Public Health

December 2001

School of Medicine
Oregon Health Science University

Certificate of Approval

This is to certify that the M.P.H. thesis of

Micah L. Thorp

has been approved

[redacted]
Donald F. Austin, M.D., M.P.H.

[redacted]
Cynthia D. Morris, Ph.D., M.P.H.

[redacted]
Angelo DeMattos, M.D.

[redacted]
Lori C. Lambert, M.A.

Table of Contents

Acknowledgments

This study could not have been completed without the assistance and support of numerous individuals. The Oregon Health Sciences University Renal Transplant Team provided extensive assistance and encouragement. Dr. John Prather provided access and insight to the Renal Transplant Database. Dr. Angelo DeMattos and Dr. Douglas Norman provided much of the knowledge and insight that helped define the problems that are addressed in this study. The extremely tolerant and patient renal transplant nurse coordinators provided assistance in locating charts. Thanks to all.

Dr. DeMattos, Dr. Cynthia Morris, Dr. Donald Austin and Lori Lambert helped with data analysis issues and Dr. Michael Ison labored next to me through exhaustive chart reviews. Dr. Austin's careful oversight of the entire project has made it enjoyable and educational. Your help was greatly appreciated.

Finally, I would like to specifically thank my friend and mentor, Dr. Angelo DeMattos without whom this endeavor would never have been undertaken.

Abstract

Human cytomegalovirus (CMV) is the most common viral infection following renal transplantation and is associated with symptomatic tissue invasive disease and acute graft rejection. Previous studies have shown that gancyclovir prophylaxis is effective in preventing tissue invasive disease in high-risk patients. Data is limited regarding CMV disease and acute rejection following discontinuation of prophylaxis. An alternative method of decreasing CMV disease is CMV seromatching donor and recipients to decrease the number of high-risk patients.

A retrospective chart review of 858 consecutive renal transplant recipients at Oregon Health Sciences University Hospital between January 1, 1990 and December 31, 1998 was conducted. Extracted data included induction immunosuppressive regimen, panel reactive antigen, CMV status of recipient and donor (as determined by IgG and IgM), graft survival, patient survival, CMV prophylaxis, first episode of acute rejection and presence of symptomatic CMV disease. Clinical symptoms and positive CMV IgM determined presence of CMV disease. Acute rejection was diagnosed by renal biopsy. A Cox proportional hazards model was used to compare symptomatic CMV infections and acute rejections between patients given gancyclovir prophylaxis and those not given gancyclovir.

Following March 1, 1996 OHSU began CMV matching donors and recipients. Data was collected from 553 patients in the pre matching period and 61 patients in the post-matching period. Chi square statistic and a logistic regression model were used to compare symptomatic CMV infections between matched and unmatched groups.

Fifty-three cases of tissue invasive CMV disease were found. A statistically significant ($p<.001$) majority of cases were in the high-risk (donor CMV positive, recipient negative) group. Univariate analysis revealed CMV risk group and presence of acute rejection predicted symptomatic CMV infection. Age at transplantation, gancyclovir prophylaxis and presence of symptomatic CMV infection predicted acute rejection. In the multivariate model patients who received gancyclovir prophylaxis experienced a delay in the development of CMV disease but did not experience a lower rate than those not receiving prophylaxis did. Patients who received gancyclovir experienced a statistically significant lower rate of acute rejection than those who did not.

In the pre-matching era there were 25 cases of symptomatic CMV. In the post matching period 3 cases were found. Using the chi square statistic there was no significant difference in symptomatic CMV infection rates between those who were matched and those who were not. In the logistic regression model, CMV matching was not statistically significant ($p = .242$).

CMV prophylaxis with gancyclovir is effective in delaying the incidence of CMV infection during first three months following renal transplantation. Gancyclovir prophylaxis did not benefit patients beyond the initial three-month period with regard to symptomatic CMV disease. CMV matching does not decreases the rate of symptomatic CMV infection. Gancyclovir had no effect on decreasing the rate of symptomatic CMV, but does decrease the rate of acute rejection.

Introduction

In the United States there are approximately 350,000 individuals who suffer from end stage renal disease (ESRD). Two therapeutic modalities, dialysis and renal transplantation, are available with which to treat this population. A comparison of these options reveals that renal transplantation is more cost effective, increases longevity and leads to greater quality of life.[1] Unfortunately, transplanted kidneys often function for a limited period of time. Thus, improving graft longevity will reduce the burden of ESRD on individual patients and society at large.

A major concern regarding renal transplant allografts is acute rejection of the transplanted kidney by the recipient. It is believed that allograft rejection is more likely to occur if the recipient develops a symptomatic infection with cytomegalovirus (CMV) following transplantation.[2] Such an infection usually arises in one of two situations: 1) a kidney infected with CMV is transplanted into a CMV negative host, (high risk), or 2) the host is CMV positive. When the host is CMV positive, symptomatic infection may arise as a result of immunosuppression therapy following the transplant (moderate risk). No infection is expected when both the kidney allograft and the recipient are CMV negative (low risk).[2]

In order to reduce the risk of an active CMV infection following renal transplant, there are two strategies. The first strategy is to attempt to match the donor kidney to the recipient with respect to CMV status, resulting in a low or moderate risk procedure. While clinically desired, this match is not always possible.

The second strategy is to prescribe gancyclovir, an antiviral chemotherapeutic agent, following the transplant to suppress any infection. However, gancyclovir prophylaxis is

only given for a limited period of time following transplantation (one to three months). It is possible that any beneficial effect lasts only as long as gancyclovir is being given and that following cessation of the gancyclovir, the risk of CMV infection is again as it was before treatment. This possibility has not been examined.

Though it is generally accepted that gancyclovir reduces the risk of active CMV infection, at least during the months of administration, another outcome of interest, and the clinical reason for attempting to actively reduce the risk of CMV infection, is graft rejection. Whether the gancyclovir ultimately protects against or delays graft rejection has also not been determined.

Human Cytomegalovirus Pathogenesis

Human cytomegalovirus (CMV) is a beta herpesvirus with a DNA genome of 230 kilobase pairs. The genome codes for approximately 200 proteins, making it nearly one and one half times as large as other herpes viruses.[3] The enlarged genome allows the virus unique adaptation to infection and survival within the human host.

Viral genes appear to be temporally regulated with three phases of gene expression. Immediate early genes encode nuclear proteins with active viral and (possibly) cellular genes. Early genes primarily encode viral DNA polymerases that begin the process of viral DNA replication. Finally, late genes encode the structural proteins of the viron.[4] These phases of viral production combined with immune evasion mechanisms make CMV an exceptionally successful human virus, avoiding both immunological and clinical detection.

Epidemiology and Transmission in the General Population

Cytomegalovirus infects large segments of the worldwide population. The prevalence of antibodies to CMV varies between 40 and 80% in countries throughout the world.[5] A

variation in distribution has been attributed to socioeconomic differences in affected populations. In many developing countries, CMV infections occur early in life and by adulthood the entire populace may be infected.[6]

CMV is spread either horizontally by close contact or vertically by intrauterine transmission. CMV has been found in a variety of bodily fluids, including pharyngeal secretions, breast milk, vaginal secretions, blood, urine and semen. The presence of the virus in so many bodily fluids leads to transmission through a variety of routes. Vertical transmission is thought to occur in 0.4-2.3% of all live births, either transplacentally or via an ascending genital route.[7] During childhood CMV is often acquired via social contacts. Studies of day care centers have shown close personal contact leads to transmission from child-to-child and parents-to-children. After puberty, CMV is often transmitted through sexual contact.[8]

Infection and Latency in Immunocompetent Hosts

Once transmitted, CMV is spread via a variety of leukocytes. During the viremic phase CMV disseminates over days and weeks to nearly every organ in the body. In immunocompetent hosts, this period of dissemination is usually asymptomatic. Within a few days, humoral and cellular responses to the infection can be detected. T-lymphocytes and natural killer cells provide the most important protective immunity and are responsible for clearing the virus from the blood stream.[9]

Following the viremic phase, CMV persists within blood cells despite humoral and cellular efforts to clear it from the body. This intractability exists even among immunocompetent patients. Immune escape mechanisms employed by the virus include the use of a class I homologue that binds beta-2 microglobulin preventing viral

presentation to the MHC class I-restricted T lymphocytes.[10] Other strategies include exposure of Fc receptors on the surface of the viral infected cell, leading to binding of IgG and subsequent prevention of lysis.[11] These and other means of molecular camouflage allow the virus to exist within cells even in the presence of a competent activated immune system.

Individuals receiving blood transfusions have high rates of immunoconversion, providing evidence of the intractability of the virus, even among immunocompetent hosts. Conversion rates fall if a leukofilter is applied during the transfusion, suggesting the importance of a CMV leukocyte reservoir in sustaining or transmitting latent CMV.[12]

During latency, CMV viral transcripts are undetectable. The only indications of viral presence are CMV antibodies and CMV-DNA, detectable by PCR. Using the PCR techniques, CMV-DNA has been located in a variety of tissues during the latency period, including smooth muscle cells, splenic tissue and bone marrow.[13] Like other latent herpes viruses, CMV persists at either undetectable replication rates or in a non-detectable state for the lifetime of the host.[12]

CMV Transmission among Immunosuppressed Organ Transplant Recipients

CMV has infected, but remains latent, in approximately 50% of the general population. Despite its high prevalence, CMV disease is a rare clinical manifestation of infection in immunocompetent individuals. Those individuals at risk for CMV disease include HIV infected patients, those receiving chemotherapeutic agents and transplant recipients.[6] Clinically significant CMV infections occur almost exclusively in immunocompromised individuals. Patients suffering from AIDs or requiring chronic

steroid use are the most frequently afflicted. In these populations, CMV constitutes a major cause of morbidity, affecting a variety of organ systems.[14]

Among solid organ transplant recipients there are four epidemiological patterns of CMV infection. (1)Primary CMV infection occurs when a seronegative transplant recipient is infected via latent virus in the transplanted organ. (2)Reactivation CMV infection occurs when a CMV seropositive transplant recipient develops active infection not from a newly acquired virus, but from reactivation of their own previously latent virus in the presence of immunosuppressive therapy. (3)Superinfection occurs when a seropositive recipient receives a seropositive organ and the virus that is activated is of donor rather than recipient origin. (4)Finally, a seronegative individual may acquire a new primary infection from the usual environmental sources of horizontal transmission.[15] Table 1 summarizes this information.

Ninety percent of infections in seronegative recipients receiving a seropositive kidney are primary infections from the infected graft. Nearly two thirds of these newly infected individuals will develop symptomatic disease. Interestingly, not all seropositive donors appear equally able to transmit the virus. Studies of different seronegative recipients receiving organs from the same seropositive donor reveal that if one recipient develops a primary infection, all do. Conversely, some seropositive donors never transmit the virus, despite multiple organ donations.[16,17]

Evidence of reactivation infection can be found in nearly all transplant recipients, if very sensitive techniques are used. Unlike primary infection, less than 20% develop clinically significant disease.[16]

Restriction enzyme techniques have shown that approximately half of CMV reactivation in seropositive recipients receiving seropositive organs is from the transplanted organ. It is estimated that approximately 40% of patients with reactivation will develop clinically significant disease.[18]

Less than 5% of CMV infections in transplant recipients are the result of new environmentally acquired primary infections. The rate of infection and the likelihood of symptomatic disease in these individuals is largely unknown, however, it is felt to differ little from the rest of the community.[16]

The most significant risk factor affecting the reactivation of CMV is the type of immunosuppression employed. Prior to the use of azathioprine and cyclosporin, CMV reactivation was largely unknown. The mechanism of immunosuppression and the intensity both appear to play a role in reactivation. Steroids alone have a limited effect on reactivation. Cyclosporin has minimal effects on reactivation, but blocks the host response to replicating virus. Anti-lymphocytic globulins markedly increase the likelihood of reactivation, irrespective of whether they are monoclonal or polyclonal. This is particularly apparent among patients at risk for CMV infection via reactivation (seropositive organ/seronegative recipient).[16,19]

The Effect of CMV Infection on Renal Transplant Recipients

Reactivation of CMV or new primary infection can have a devastating impact on those affected. A wide variety of organ systems can become clinically dysfunctional when CMV begins to actively replicate. If not initially suspected, CMV is difficult to diagnose. Nonspecific prodromal symptoms, a prolonged fever, arthralgias, anorexia, myalgias, lasting two to four weeks are often the primary sequelae of disease. In addition to these

prodromal symptoms, thrombocytopenia and leukopenia are common. Organ specific disease may take a variety of forms. Hepatitis, pneumonitis, colitis, myocarditis, esophagitis, encephalitis, gastroenteritis and chorioretinitis are all specific sequelae of CMV infection that may follow or occur during the prodromal period.[20]

CMV infection is associated with acute graft rejection. It is both a cause and an effect of rejection resulting from a complex interplay of cytokines and interleukins that is poorly understood. A variety of T-cell stimulatory pathways known to be activated by CMV have been implicated in the pathogenesis of acute rejection. A number of cohort studies have shown a significant relationship between CMV and acute rejection. Further evidence includes the observation that patients at high risk of CMV are more likely to develop acute rejection.[2] In addition, patients with other severe illnesses can induce the onset of a CMV infection simply through the activation of common mediators of inflammation. Thus it is often difficult to discern in very ill patients with CMV disease whether the illness or CMV disease occurred first.

CMV Prophylaxis in Renal Transplantation

Gancyclovir is a nucleoside analog shown to be effective in treating CMV infection at a dose of one gram three times per day for 14 to 30 days depending on the nature of the infection. In an effort to curtail the number of CMV infections following renal transplantation, the administration of gancyclovir during the immediate postoperative period has been advised.[21] While evidence exists that prophylaxis is effective during the period of administration, little evidence exists regarding any long-term benefit. It has been suggested that gancyclovir may merely delay the onset of CMV infection rather than prevent it. This was demonstrated in 1994 by Reinke, when in the course of a study

of CMV and allograft dysfunction, he found that patients treated with gancyclovir did not develop CMV infections while it was being administered, but began developing CMV infections immediately following discontinuation.[22] Despite the lack of evidence for long term benefits, the American Society of Nephrology currently recommends post operative gancyclovir prophylaxis for renal transplant recipients.[21]

The use of gancyclovir is associated with some adverse risks. Gancyclovir frequently induces granulocytopenia, thrombocytopenia and neurological dysfunction. In addition, it is quite expensive, adding substantial cost to the renal transplant procedure.[23] For these reasons it is important to discern whether or not gancyclovir prophylaxis has a role in renal transplantation.

The most common mechanism by which renal transplant recipients develop CMV infection results from the reactivation of the virus in a CMV infected kidney transplanted into a recipient who had not been infected before the transplant. There is no risk of reactivation if both donor kidney and recipient are seronegative prior to transplantation, as neither harbors the virus. Recipients who are seropositive are considered at moderate risk for reactivation regardless of the serostatus of the transplanted kidney.[24] A strategy to reduce the number of high-risk recipients (donor kidney is CMV positive, recipient is CMV negative) is to match CMV negative kidneys with CMV negative recipients. This matching of seronegative cadaveric kidneys and seronegative recipients would increase the number of low risk transplants and decrease the number of high-risk transplants. The strategy could only be applied to cadaveric transplants, since the benefit of having a living donor far outweighs the detriment imposed by the increased likelihood of developing CMV. There is little information on the efficacy of such a matching strategy.

Patients with symptomatic CMV infections are more likely to develop acute rejection and decrease the life span of the graft. The purpose of this study is to investigate the efficacy of gancyclovir prophylaxis and serologic matching in decreasing symptomatic CMV infections. In addition, the study examines whether gancyclovir prophylaxis decreases the rate of acute rejections. The results may provide future direction in decreasing the untoward effects of CMV in renal transplant recipients, thus improving the longevity of the transplanted kidney.

Table 1

Methods of infection and associated CMV risk groups

Method of infection	**Definition**	**Affected Donor and Recipient CMV status**
1. Primary Infection	Recipient is CMV –, but receives new CMV infection from CMV infected kidney	Donor + / Recipient – (high risk)
2. Reactivation	Recipient's latent CMV infection is reactivated	Donor ± / Recipient + (moderate risk)
3. Superinfection	Recipient is CMV +, but receives CMV infection from CMV infected kidney	Donor + / Recipient + (moderate risk)
4. "New" Primary infection	Recipient acquires new infection from environment	Donor ± / Recipient ± (high, moderate, low risk)

References

1. Wolfe RA, Ashby VB, Milford EL, et.al.. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first transplant. New England Journal of Medicine. 341:1725-1730. 1999.

2. Fishman JA, Rubin RH. Infection in Organ-Transplant Recipients. N Engl J Med. 338:1741-1751. 1998.

3. Chee MS, Bankier AT, Beck S, et.al.. Analysis of he protein-coding content of the sequence of human cytomegalovirus strain AD169. Curr Topic Microbiol Immunol 154:126-169. 1990.

4. Sissons JG, Sinclair JH, Borysiewicz LK. Pathogenesis of human cytomegalovirus disease and the kidney. Kid International. 40:S8-S12. 1991.

5. Demmler GJ. Summary of a workshop on surveillance for congenital cytomegalovirus disease. Rev Infect Dis. 13:315-329. 1991.

6. Wang PS, Evans AS. Prevalence of antibodies to Epstein-Barr virus and cytomegalovirus in sera from a group of children in the People's Republic of China. J Infect Dis. 153:150-152. 1986.

7. Hirota K, Muraguchi K, Watabe N, et.al.. Prospective study on maternal intrauterine and perinatal infections with cytomegalovirus in Japan during 1976-1990. J Med Virol. 37:303-306. 1992.

8. Pass RF, Hutto SC, Ricks R, et.al.. Increased rate of cytomegalovirus infection among parents of children attending day-care centers. N Engl J Med. 314:1414-1418. 1986.

9. Bruggeman CA. Cytomegalovirus and latency: an overview. Virchows Archiv B. 64:325-333. 1993.

10. Browne H, Smith G, Beck S, et.al.. A complex between MHC class 1 homologue encoded by human cytomegalovirus and ∃2 microglobulin. Nature 347:770-772. 1990.

11. Bin X, Tsugiya M, Ishida K, et.al.. Characterization of IgG Fc receptors induced by human cytomegalovirus. J Gen Virol. 70:893-900. 1989.

12. Lang DJ, Ebert PA, Rodgers BM, et.al.. Reduction of postperfusion cytomegalovirus-infections following the use of leukocyte depleted blood. Transfusion. 17:391-395. 1977.

13. Klotman ME, Henry SC, Greene RC, et.al.. Detection of mouse cytomegalovirus nucleic acid in latently infected mice by in vitro enzymatic amplification. J Infect Dis. 161:220-225. 1990.

14. Hibberd PL, Snydman DR. Cytomegalovirus infection in organ transplant recipients. Infect Dis Clinics of N America. 9:863-877. 1995.

15. Rubin RH. Cytomegalovirus disease and allograft loss after organ transplantation. Clinical Infectious Diseases. 26(4):871-873. 1998.

16. Rubin RH. Infection in the renal and liver transplant patient. In: Rubin RH, Young LS, eds. Clinical approach to infection in the compromised host. 2nd ed. New York: Plenum Publishing, 557-621. 1988.

17. Betts RF, Freeman RB, Douglas RG Jr, et.al.. Transmission of cytomegalovirus infection with renal allograft. Kidney Int. 8:385-392. 1975.

18. Chou SW, Norman DJ. The influence of donor factors other than serological status on transmission of cytomegalovirus to transplant recipients. Transplantation. 46:89-93. 1988.

19. Rubin RH, Tolkoff-Rubin NE, Oliver D, et.al.. Multicenter seroepidemiologic study of the impact of cytomegalovirus infection on renal transplantation. Transplantation. 40:243-249. 1985.

20. Bilgin N, Karakayali H, Moray G, et.al. Incidence of Cytomegalovirus Infection in Kidney Recipients. Transplantation Proceedings. 28(4):2314-2315. 1996

21. Jassal SV, Roscoe JM, Zaltzman JS, et.al. Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation. JASN 9(9): 1697-1708. 1998.

22. Reinke P, Fietze E, Ode-Hakim, et.al. Late-acute renal allograft rejection and symptomless cytomegalovirus infection. Lancet. 344:1737-1738. 1994

23. Wright FH, Banowsky LH. Cytomegalovirus infection and prophylaxis in renal transplantation: financial consideration. Transplant Proc. 30:1318-1319. 1998.

24. Bilgin N, Karakayali H, Moray G, et.al. Incidence of cytomegalovirus infection in kidney recipients. Transplantation Proceedings. 28(4):2314-2315. 1996.

Methods

Specific Aims

There are three specific aims of this study.

The Effect of Gancyclovir Prophylaxis on Symptomatic CMV Infections

Specific aim 1 is to determine whether prophylactic administration of gancyclovir delays or prevents the occurrence of *symptomatic cytomegalovirus infections* in renal transplant recipients.

The Effect of Serological CMV Matching on Symptomatic CMV Infections

Specific aim 2 is to assess the effect of cytomegalovirus matching of renal allograft donors and recipients on *symptomatic cytomegalovirus infection* rates.

The Effect of Gancyclovir Prophylaxis on Acute Rejection

Specific aim 3 is to determine whether prophylactic administration of gancyclovir delays or prevents the occurrence of *acute rejection* in renal transplant recipients.

Hypotheses:

The Effect of Gancyclovir Prophylaxis on Symptomatic CMV Infections

A. It is hypothesized that gancyclovir prophylaxis delays, but does not prevent, the occurrence of symptomatic cytomegalovirus in renal transplant recipients.

The American Society of Transplantation currently recommends prophylaxis be administered to prevent symptomatic cytomegalovirus infection during the three months immediately following transplantation.[7]

The Effect of Serological CMV Matching on Symptomatic CMV Infections

B. It is hypothesized that matching cytomegalovirus IgG negative kidneys with cytomegalovirus negative recipients decreases the incidence of symptomatic cytomegalovirus infections.

Matching increases the number of recipients at low risk to develop cytomegalovirus infection, and decreases the number of recipients at high risk. This redistribution is expected to decrease the incidence of symptomatic cytomegalovirus infection among cadaveric recipients.

The Effect of Gancyclovir Prophylaxis on Acute Rejection

C. It is hypothesized that gancyclovir prophylaxis delays or prevents acute rejection in renal transplant recipients. Symptomatic cytomegalovirus infections are associated with an increased risk of acute rejection.[3] Gancyclovir prophylaxis delays or reduces acute rejection episodes.

Subjects

In order to address the specific aims of this study, a retrospective cohort study was conducted. All adult patients transplanted at OHSU between January 1, 1990 and December 31, 1998 with a first time solitary kidney transplant were initially included (n = 896). The period was chosen (1) to ensure all patients were transplanted following the institution of cyclosporin as a potential immunosuppressant medication and (2) to allow a two year follow up period for all patients. Patients were identified using the OHSU Renal Transplant Database.

Due to differences between adults and children in immunosuppressive regimens, original kidney disease, and likelihood of preceding CMV exposure, children (age < 18

years) were excluded from the study. Since multiple organ transplants alter the potential for post-transplant exposure to CMV, patients transplanted with other organs simultaneously to a kidney transplant were excluded from this study. One individual who was lost to follow up was included. Additional inclusion criteria for individuals were that initial adequate renal function of the allograft was required and, if death occurred, a prior assessment of CMV serology and symptomatology status was required, as well as acute rejection status.

Inclusion criteria resulted in 38 individuals being excluded. Among the 38 excluded, 27 died without a prior determination of rejection status. Fourteen patients expired secondary to cardiac complications, eight from multiple organ system failure and five from unclear etiologies. The remaining eleven suffered from graft failure but did not die. All were diagnosed with either immediate acute rejection or delayed graft function. It is unclear whether CMV was associated with any death or graft failure.

Those who died in the two years following transplantation, did so primarily from illnesses thought unrelated to CMV. Unfortunately, CMV status was never checked prior to patient deaths, so it is unclear which outcome group (symptomatic CMV infection or no symptomatic CMV infection) they should be assigned to. The proportion of patients who died given gancyclovir prophylaxis (8%) was similar to the proportion of patients given gancyclovir in the total population (12%). This suggests that coding these patients as though they had developed CMV infections or not developed CMV infections would not have significantly altered the outcome of the study. In order to assess whether or not a change might occur, the patients who died were reinserted into the final Cox hazards model of the gancyclovir and symptomatic CMV infection analysis as though they had

not developed a symptomatic CMV infection at the time of death. The results revealed no change in significance.

The primary etiology of graft failure was delayed graft function. In these cases patients received a graft which never adequately functioned. Thus patients with graft loss never had the opportunity to develop either outcome of interest (symptomatic CMV infection or acute rejection).

Database

The Oregon Health Sciences University Renal Transplant Database contains information regarding all adult renal transplants performed at the University from 1980 to the current day. Information in the database includes the date of transplantation, patient demographics (age, etiology of renal failure, etc.), kidney donor and recipient CMV serostatus, induction immunosuppression, medications administered at the time of transplantation, acute rejection episodes and graft loss. Information at the time of discharge is collected by nurse coordinators and subsequently recorded in the database. Following transplantation, all patients are seen in the transplant clinic weekly for one month, every other week for two months then monthly for one year. Nurse coordinators collect information at each clinic visit. Confirmation of CMV disease is made by subsequent culture of blood or affected tissue. Suspected episodes of CMV disease are recorded in the patient's chart.

Patient labs and hospital admissions at outside institutions are monitored by nurse coordinators throughout the two years following transplantation. These data are recorded in the database.

Prior to March 1, 1996, the OHSU renal transplant program did not have a protocol in place to determine which patients were to receive gancyclovir prophylaxis. As a result, some were exposed to the prophylactic regimen and others were not. Those who received gancyclovir prophylactically received it for one to three months. Gancyclovir prophylaxis was recorded in the patient's chart, but was not a part of the database.

Assessment of Determinants

The Effect of Gancyclovir Prophylaxis on Symptomatic CMV Infections

To address Hypothesis A above, patient records were reviewed to determine whether CMV disease occurred over the subsequent two years following transplantation. CMV was ascertained by clinical suspicion at time of patient presentation. Definition of disease included evidence of symptoms and positive CMV culture results. In the event a culture could not be confirmed, the patient was classified as "not diseased".

Cohort status was determined by notation of gancyclovir prophylaxis obtained by a review of the patient's medical record. A patient was coded as "exposed" gancyclovir was received for at least thirty days following renal transplant. Otherwise, patients were classified as "unexposed". Patients who received prophylaxis (n = 100) had received gancyclovir, but if they had failed to receive at least thirty days of gancyclovir prophylaxis were classified as "unexposed" (n = 7). The gancyclovir was stopped in this group of patients due to drug intolerance or adverse effect. The adverse event in 5 patients was leukopenia. One patient had nausea and vomiting attributed to the drug. One patient's gancyclovir was stopped for unclear reasons. The average period of gancyclovir administration for those patients given less than 30 days was 4.4 days. Patients who received at least 30 days or more were classified as "exposed" (n = 93).

Patients' exposure classification was fixed and once a part of either cohort, they were not moved to the other (closed cohorts). A Cox proportional hazard model was used to assess differences in time to symptomatic CMV infection comparing individuals that received gancyclovir with those that did not.

The Effect of Serological CMV Matching on Symptomatic CMV Infections

On March 1, 1996, OHSU began matching cadaveric kidneys and recipients by CMV IgG serostatus. To assess Hypothesis B, a continuous cohort of patients who received cadaveric kidneys from the period immediately preceding March 1, 1996 was designated "unmatched" (n = 553). A continuous cohort of patients from a period of time immediately following this date was designated "matched" (n = 61). Cases of symptomatic cytomegalovirus infection were identified for each recipient in a two-year period following transplantation. The definition of disease required both evidence of symptoms and positive CMV culture results. Suspected CMV disease without positive culture results were classified as "not diseased". CMV cultures noted in the patient's chart were confirmed via the OHSU electronic medical record. A Pearson's chi square test of homogeneity was used to compare the incidence of symptomatic CMV infection between the CMV "matched" and CMV "unmatched" cohorts. In addition, a logistic regression model was created to assess the "matched" and "unmatched" cohorts.

The Effect of Gancyclovir Prophylaxis on Acute Rejection

To address Hypothesis C, cohort status was determined by notation of gancyclovir prophylaxis or lack of prophylaxis in the database, as was confirmed by a review of the patient's medical record.

Patient records were searched to determine whether an episode of acute rejection occurred over the two years following the patient's transplant. Definition of rejection was increasing serum creatinine and biopsy evidence of rejection. Patients were classified based on the presence of a single rejection episode during the two year following transplantation. A patient's exposure classification was fixed and, once a part of either cohort, a patient was not moved to the other (closed cohorts). A Cox proportional hazard model was used to assess differences in time to rejection between "exposed" and "unexposed" cohorts comparing individuals that received gancyclovir and those who did not.

Outcomes Definitions

Symptomatic Cytomegalovirus infections were defined by the presence of a positive CMV IgM serology in association with either the prodromal syndrome (fever, arthralgias, myalgias, anorexia, night sweats) or one of the following:

1) neutropenia
2) esophogitis
3) hepatitis
4) pneumonitis
5) chorioretinitis
6) colitis
7) myocarditis
8) gastroenteritis

Acute allograft rejections were defined as any allograft biopsy meeting Banff[1] criteria as determined by a renal pathologist. Cases were biopsied if their creatinine rose more than 20% from baseline for at least 4 days and remained elevated for more than a few days.

Gancyclovir prophylaxis was defined as the administration of gancyclovir (intravenously or orally) for a period of time at least thirty days immediately following transplantation.

Variables

The following variables were extracted from all patients age 18 or greater at the time of their first renal transplant. Variables are listed on Table 2.

1) Age. All patients were age 18 or over. There was no maximum age.
2) Date of Transplant. All transplants were performed between January 1, 1990 and December 31, 1998.
3) Date of First Acute Rejection Episode. First recorded date of acute rejection diagnosis confirmed by transplant biopsy.
4) CMV Serostatus of donor kidney (IgG). Pre transplant IgG CMV serostatus (positive or negative) as recorded in transplant database.
5) CMV Serostatus of recipient kidney (IgG). Pre transplant IgG CMV serostatus (positive or negative) as recorded in transplant database.
6) Original disease. Twenty-three diagnoses were coded. They included chronic glomerulonephritis, focal segmental glomerulonephritis, membranoproliferative glomerulonephritis, membranous glomerulonephritis, Goodpasture's syndrome, IgA

[1] Solez K, Benediktsson H, Cavello T, et.al. Report of the Third Banff Conference on Allograft Pathology (July 20-24, 1995) on classification and lesion scoring in renal allograft pathology. Transplant

nephropathy, Lupus nephritis, Wegner's granulomatosis, Henoch-Schloen's purpura, medullary cystic disease, polycystic kidney disease, Alport's syndrome, interstitial nephritis, hypertensive nephroscherosis, amyloid, hemolytic uremic syndrome, reflux nephropathy, diabetic nephropathy, post-infectious glomerulonephritis, Wilm's tumor, cyclosporin/tacrolimus toxicity, unknown etiology and other disease. As diabetes has been associated with acute rejection rates, a categorical variable was created designating the original disease as either "diabetes" or "not diabetes".

7) Induction therapy. Ten different induction protocols were identified. They were coded based as either "antilymphocytic therapy" or "non-antilymphocytic therapy". Antilymphocytic therapies include antithymocyte globulin, anti-CD3 (hum 291), Minnesota antilymphoblast globulin, OKT3 (muromonab), anti-IL2-R (simulect), thymoglobulin, anti-IL2-R (daclizumab), OKT4-A. Non-antilymphocytic therapy included intravenous cyclosporin A or no therapy.

8) Age at Transplantation. Age in years as recorded in transplant database.

9) Cadaveric or Living Related Donor Kidney. Origin of donated kidney as recorded in transplant database.

10) Panel-reactive antigen. Results were coded as high-risk if the PRA was greater than 20, or low-risk if PRA was 20 or less.

11) Date of graft failure.

12) Date of death.

In addition to information extracted from the renal transplant database the following variables were obtained via chart review. One reviewer reviewed each chart.

Proc 1996; 28:441.

Information was entered into computer database. Reviewers were not blinded to patient cohort.

13) Anti-CMV Prophylaxis. Results were coded as "prophylaxis" if gancyclovir had been given for at least 30 days following transplantation or "no prophylaxis" if acyclovir, valcyclovir, gancyclovir for less than 30 days or nothing had been given following transplantation.

14) Date of acute rejection. The date of the biopsy that revealed acute rejection was recorded. Only the first rejection following transplantation was used for this analysis.

15) Date of symptomatic CMV infection. Using the case definition described previously, cases of post-transplant symptomatic CMV infection were recorded on the date in which the symptoms first appeared as recorded in the chart.

All patients lost to follow-up were included in the groups in which they were initially assigned.

Data Management

Following download from the OHSU renal transplant database into SPSS, and subsequent entry of chart review data, a Cox Proportional Hazards Model was created assessing the effect of gancyclovir prophylaxis on time to symptomatic CMV infection, and time to acute rejection. After data were entered, identifying documentation linking patients' medical record numbers to computer generated identification was destroyed.

Statistical Methods

The Effect of Gancyclovir Prophylaxis on Symptomatic CMV Infections

The following variables were analyzed in Cox proportional hazards univariate models assessing differences in time to symptomatic CMV between patients who received gancyclovir and those who did not (Table 2):

1. Panel reactive antigen was analyzed as a categorical variable, "high" or "low" as noted previously.
2. Original kidney disease was analyzed as a categorical variable, "diabetes" or "not diabetes" as noted previously.
3. Age at transplantation was analyzed as a continuous variable in .01 year increments.
4. Induction therapy was analyzed as a categorical variable, "antilymphocytic therapy" or "no antilymphocytic therapy".
5. Acute rejection episode was analyzed as a categorical variable, "rejection" or "no rejection".
6. CMV risk groups were analyzed as a categorical variable "high", "moderate" or "low". Categories were created based on the CMV serostatus. "High" risk patients were those whose CMV IgG was negative and received a CMV IgG positive kidney. "Moderate" risk patients were those who were CMV IgG positive and received either a CMV IgG negative or positive kidney. "Low" risk patients were those who were CMV IgG negative and received a CMV IgG negative kidney.
7. Cadaveric/Living donor status was analyzed as a categorical variable.
8. Gancyclovir prophylaxis was recorded as "prophylaxis or no prophylaxis".

Statistically significant variables ($p < .20$) in univariate models were selected to be included in the final model. Time to symptomatic CMV infection was calculated for the

first two years, and patients were considered failed if a CMV infection occurred. One patient lost to follow up was censored. Gancyclovir and non-gancyclovir strata were incorporated in the model.

The Effect of Serological CMV Matching on Symptomatic CMV Infections

The number of symptomatic CMV infections in "matched" and "non-matched" patients were compared using a Pearson's chi square test of homogeneity. A logistic regression model was then created. The following variables were placed in the model:

1. Panel reactive antigen was analyzed as a categorical variable, "high" or "low" as noted previously.
2. Age at transplantation was analyzed as a continuous variable.
3. Induction therapy was analyzed as a categorical variable, "antilymphocytic therapy" or "no antilymphocytic therapy".
4. CMV risk groups were analyzed as a categorical variable "high", "moderate" or "low". Categories were created as described above.
5. Cadaveric/Living donor status was analyzed as a categorical variable.
6. Original kidney disease was analyzed as a categorical variable, "diabetes" or "not diabetes" as noted previously.
7. Acute rejection episode was analyzed as a categorical variable, "rejection" or "no rejection".

Statistically significant variables ($p < .20$) in univariate models were selected to be included in the final model.

The Effect of Gancyclovir Prophylaxis on Acute Rejection

A Cox proportional hazards model was created assessing the effect of gancyclovir prophylaxis on time to acute rejection. The following variables were placed in univariate models:

1. Panel reactive antigen was analyzed as a categorical variable, "high" or "low" as noted previously.
2. Original kidney disease was analyzed as a categorical variable, "diabetes" or "not diabetes" as noted previously.
3. Age at transplantation was analyzed as a continuous variable.
4. Induction therapy was analyzed as a categorical variable, "antilymphocytic therapy" or "no antilymphocytic therapy".
5. Symptomatic CMV infections were analyzed as categorical variables, "infected" or "not infected", based on the criteria listed previously.
6. CMV risk groups were analyzed as a categorical variable "high", "moderate" or "low". Categories were created as described above.
7. Cadaveric/Living donor status was analyzed as a categorical variable.
8. Gancyclovir prophylaxis was recorded as "prophylaxis or no prophylaxis".

Statistically significant variables ($p < .20$) in univariate models were selected to be included in the final model. Time to symptomatic acute rejection was calculated for the first two years. Gancyclovir and non-gancyclovir strata were incorporated in the model.

Table 2

Variable Coding

Variable	Code
Age at Transplantation	Years in .01 years
CMV Risk Group	High = 3 Moderate = 2 Low = 1
Original Kidney Disease	Diabetes = 1 Other kidney disease = 0
Induction Therapy	Antilymphocytic Therapy = 1 No antilymphocytic Therapy = 0
Cadaveric/Living Related Donor	Cadaveric = 1 Living Related = 0
Panel Reactive Antigen	High (> 20) = 1 Low ($\leq$ 20) = 0
Time to Symptomatic CMV Infection	Years in .01 increments
Anti-CMV Prophylaxis	Gancyclovir = 1 No gancyclovir = 0
Time to Acute Rejection	Years in .01 increments

Results

Patient Characteristics

From a total of 896 adult patients with first time, solitary kidney transplants during the period 1990 - 1998 in the OHSU renal transplant database, 858 who did not experience initial graft failure or death unrelated to acute rejection were selected for study. One patient lost to follow-up was included. Data were available for a 24-month period following transplantation.

Among the 858 patients, the mean age at transplantation was 43.8 years with a standard deviation of 12.5 years. Ages ranged from 18 (selected as the cut point for adult cases) to 78 years. Fifty-four percent (n = 463) of patients were male, 46% (n = 395) female. A majority of patients, 87.2% (n = 748), were treated with antilymphocytic therapy. The most common etiology of renal failure was diabetes (26.6%), followed by chronic glomerulonephritis (11.9%), and polycystic kidney disease (10.7%). Among the CMV risk group categories, the CMV high-risk group (CMV IgG positive donor, negative recipient) had the smallest number of patients (n = 104). The group with the most patients was the moderate risk group (CMV IgG positive recipient) (n = 507). Other patient characteristics are listed in Table 3.

Table 4 shows that symptomatic CMV infections (positive CMV IgM with clinical evidence of CMV) were not common in the cohort study, affecting only 6.2% of patients (n = 53). Conversely, acute rejection was quite common affecting 41.6% of patients (n = 357).

Patient characteristics differed by CMV serological risk groups. Mean age was highest in the moderate risk group (45.7 years) and lowest in the high-risk group (35.9

years, $p < .001$) (Table 5). Diabetes prevalence differed significantly ($p < .001$) among the three risk groups with the greatest prevalence among patients in the low risk group (35.2%) and the lowest prevalence in the high-risk group (13.5%, $p < .001$).

Additionally, CMV serological risk groups were predictive of symptomatic CMV infection ($p < .001$). Twenty-seven percent of patients in the high-risk group, 4.9% of patients in the moderate risk group and no patients in the low risk group (CMV IgG negative donor, negative recipient) experienced symptomatic CMV infection.

CMV serological risk groups were not predictive of acute rejection ($p = .336$), however, with 41 cases of acute rejection found in the high-risk group (43.3%), 204 cases in the moderate risk group (42.2%) and 112 cases in the low risk group (47.0%) (Table 6).

Table 7 shows patients treated with gancyclovir were more likely to have a high panel reactive antigen (14.0% vs. 7.1%, $p = .019$), less likely to have had a cadaveric donor (65.6% vs. 72.3%, $p = .176$) and slightly less likely to be diabetic (20.4% vs. 26.8%, $p = .187$). Patients without gancyclovir prophylaxis were significantly more likely to suffer an episode of acute rejection than those that did not (8.6% vs. 45.6%, $p < .001$) (Table 8). However, gancyclovir prophylaxis was not associated with a decrease in symptomatic CMV infection.

The Effect of Gancyclovir on Symptomatic CMV Infections

To further assess whether gancyclovir prophylaxis decreases symptomatic CMV infections for the two years following transplantation, a Cox proportional hazards model was constructed. Results from the initial univariate analysis of potential predictors of symptomatic CMV infection are listed in Table 9. In these models the outcome variable

"acute rejection" was included as an independent variable. Variables significantly associated with symptomatic CMV infection include presence of acute rejection ($p = .004$) and CMV symptomatic risk group ($p < .001$). Patients suffering an episode of acute rejection were more than twice as likely to develop a symptomatic CMV infection as those who did not suffer acute rejection. CMV risk group could not be used as a variable in its initial form, as the coefficients did not converge. This occurred due to the lack of symptomatic CMV infections in the low risk group. In an effort to circumvent this problem, the moderate risk group cases were combined with the low risk group cases to create a single moderate/low risk group. Compared to this combined risk group, the high-risk group was significantly associated symptomatic CMV infection ($p < .001$). High-risk patients were over ten times as likely to develop a symptomatic CMV infection as patients in the combined low and moderate risk group. Gancyclovir prophylaxis was not significantly associated with increased or decreased risk of symptomatic CMV infection in the 24 months following transplantation ($p = .187$). Additional variables that did not predict CMV infection episodes included antilymphocytic induction therapy ($p = .348$), age at transplantation ($p = .389$), diabetes ($p = .427$), cadaveric donor ($p = .235$) and high panel reactive antigen ($p = .330$).

Following the univariate analysis, multivariate analysis was conducted using variables significant ($p < .20$) in the univariate analysis. Table 10 describes the multivariate model. Variables included in the multivariate model were acute rejection, CMV risk group and gancyclovir prophylaxis. Patients in the CMV high-risk group were over nine times more likely to develop a symptomatic CMV infection than those in the moderate/low risk group after adjusting for gancyclovir use and acute rejection episodes. Those who

suffered from an episode of acute rejection were nearly twice as likely to develop a symptomatic CMV infection ($p = .020$). Figure 1 shows a similar increased likelihood of acute rejection among patients treated with gancyclovir compared to those who were not.

Fewer symptomatic CMV infections occurred in the first month following transplantation among those who received gancyclovir than those who did not. After the first month following transplantation, symptomatic CMV infections among those given gancyclovir prophylaxis increased, eventually exceeding those not given gancyclovir prophylaxis. By the end of the second year a larger percentage (6.9%) of patients who had received gancyclovir had suffered a symptomatic CMV infection than those who had not (3.5%). At no point were the differences in symptomatic CMV infections between patients given gancyclovir prophylaxis and those not given gancyclovir prophylaxis significant.

The Effect of CMV Matching on Symptomatic CMV Infections

Significant differences between the matched and unmatched groups included: 1) the percentage of patients given gancyclovir (matched 67.2%, unmatched 3.6%, $p < .001$) (Table 11), and 2) patients with acute rejection (matched 1.6%, unmatched 49.7%, $p < .001$) (Table 12). Differences not present between groups included gender ($p = .687$), high panel reactive antigen (matched 13.1%, unmatched 7.2%, $p = .104$), diabetes (matched 22.9%, unmatched 29.3%, $p = .298$) and antilymphocytic therapy (matched 86.9%, unmatched 92.6%, $p = .119$). There was little difference in the number of matched and unmatched patients between the CMV high-risk groups (matched 4.9%, unmatched 9.2%, $p = .260$). When symptomatic CMV infections were stratified by both matched status and CMV risk group (Figure 2), a difference in the percent of CMV

infections between matched CMV low risk patients and unmatched CMV low risk patients, is apparent (23% vs. 32%). This disparity is accompanied by a reduction in the prevalence of high-risk patients, which decreased from the unmatched to the matched group (9.2% vs. 4.9%).

The cohort of patients in whom CMV matching (donor and recipient matched by CMV IgG status) was applied experienced nearly the same percentage of symptomatic CMV infections (4.9%) as the cohort of patients who were not matched (4.5%). A chi square test of homogeneity by CMV match status did not show a difference in the proportion of symptomatic CMV infection ($p = .888$).

A logistic regression model was created to determine if symptomatic CMV infection was affected by matching variables after adjusting for other important predictors. The model revealed the significance of the CMV high-risk group (relative risk = 8.29, $p < .001$) and acute rejection (relative risk = .34, $p = .021$), in predicting symptomatic CMV infections. Variables which were not significant included high panel reactive antigen ($p = .403$), diabetes ($p = .385$), antilymphocytic immunosuppression ($p = .776$), gancyclovir prophylaxis ($p = .190$) and age at transplantation ($p = .996$).

When the CMV high risk and acute rejection variables were included in the model with CMV matching, a decrease in the rate of symptomatic CMV infections among matched patients was still not statistically significant (from $p = .942$ to $p = .242$).

The Effect of Gancyclovir Prophylaxis on Acute Rejection

To assess whether gancyclovir prophylaxis decreases symptomatic CMV infections a Cox proportional hazards model was constructed. The initial Cox proportional hazards univariate analyses revealed four variables that predicted acute rejection with statistical

significance ($p < .05$): symptomatic CMV infection ($p = .001$), gancyclovir prophylaxis ($p < .001$) and age at transplantation ($p = .004$). High panel reactive antigen was nearly significant (.074) and due to its biological relevance was included in the multivariate model. The CMV high-risk group was nearly significant as a predictor as well ($p = .069$) and was included in the model. Variables that were not significantly related to the outcome included the presence of diabetes ($p = .781$), antilymphocytic induction therapy ($p = .787$) and cadaveric/living donor ($p = .345$) (Table 13).

Following the univariate analyses, a multivariate analysis was conducted using those variables at $p < .20$ in the univariate analyses. Variables included in the multivariate model were *symptomatic CMV infection*, *age at transplantation*, *gancyclovir prophylaxis*, *CMV high-risk group* and *panel reactive antigen* (Table 14).

Relative risks of variables included in the final model revealed a significantly increased risk of acute rejection among patients who suffered a *symptomatic CMV infection* (RR = 1.98), a significantly decreased risk (RR = .71) in the *CMV high-risk group*, a highly significant decreased risk (RR = .14) for *gancyclovir prophylaxis*, a small but significantly decreased risk (RR = .99) for older *age at transplantation* and increased risk (RR = 1.41) for high *panel reactive antigen* of borderline significance. Patients not given gancyclovir prophylaxis were 7.1 times more likely to develop an episode of acute rejection than those given gancyclovir. Patients in the moderate and low risk groups were 1.4 times more likely to develop an episode of acute rejection than those in the high-risk group ($p = .057$).

Survival curves indicated that patients treated with gancyclovir had far fewer episodes of acute rejections than did those not given gancyclovir (Figure 3). Up to 30% of patients

not given gancyclovir had an episode of acute rejection in the first month following transplantation (the period during which the gancyclovir would have been administered, had those patients received conventional CMV prophylaxis). After the first month, the overall risk of acute rejection decreased, but the risk for those who received gancyclovir was substantially less than those who did not. Two years after transplant, patients not given gancyclovir were more than five times more likely to have developed an episode of acute rejection (45.6% vs. 8.6%, $p < .001$). This appears to primarily reflect the large difference that occurred initially following transplantation.

Table 3

Characteristics of Renal Transplant Recipients Occurring up to 24 Months Following Transplantation, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients 1990-1998

Age at Transplantation	(years)
Mean (+/- SD)	43.8 ± 12.5
Range	18-78
Gender	n (%)
Female	395 (46.0%)
Male	463 (54.0%)
Diabetes	n (%)
No	630 (73.4%)
Yes	228 (26.6%)
Panel Reactive Antigen	n (%)
High	67 (7.8%)
Low	791 (92.1%)
Donor	n (%)
Living	244 (28.4%)
Cadaveric	614 (71.6%)
Immunosuppression	n (%)
Antilymphocytic	748 (87.2%)
Not antilymphocytic	110 (12.8%)
CMV Risk Groups	n (%)
High	104 (12.1%)
Moderate	507 (59.1%)
Low	247 (28.8%)

Table 4

Study Events Occurring up to 24 Months Following Transplantation, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients 1990-1998

Acute Rejection	n (%)
Yes	357 (41.6%)
No	501 (58.4%)
Symptomatic CMV Infection	n (%)
Yes	53 (6.2%)
No	805 (93.8%)

Table 5

Characteristics of Renal Transplant Recipients by CMV Risk Group Occurring up to 24 Months Following Transplantation, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients 1990-1998

	Patients in each CMV Risk Group			Total	p-value*
	Low	Moderate	High		
Gender					
Male n(%)	128 (51.8)	283 (55.8)	52 (50.0)	463 (54.0)	.742
Female n(%)	119 (48.2)	224 (44.2)	52 (50.0)	395 (46.0)	
Age					
Mean (+/-SD)	42.4(11.6)	45.7(12.4)	35.9(12.6)	43.8(12.5)	<.001
Panel Reactive Antigen					
High n(%)	17 (6.9)	43 (8.5)	7 (6.7)	67 (7.8)	.678
Low n(%)	230 (93.1)	464 (91.5)	97 (93.3)	791 (92.2)	
Diabetes					
Yes n(%)	87 (35.2)	124 (24.5)	14 (13.5)	225 (26.1)	<.001
No n(%)	160 (64.8)	383 (75.5)	90 (86.5)	633 (73.9)	
Antilymphocytic Immunosuppression					
Yes n(%)	221 (89.5)	437 (86.2)	90 (86.5)	748 (87.2)	.441
No n(%)	26 (10.5)	70 (13.8)	14 (13.5)	110 (12.8)	
Donor					
Cadaveric n(%)	180 (72.9)	380 (75.0)	54 (51.1)	614 (71.6)	<.001
Living n(%)	67 (27.5)	127 (25.0)	50 (48.9)	244 (28.4)	
Gancyclovir Prophylaxis					
Yes n(%)	7 (2.8)	70 (13.8)	16 (15.3)	93 (10.8)	<.001
No n(%)	240 (97.2)	437 (86.2)	88 (84.7)	765 (89.2)	

*Discrete variables assessed via chi-square test of independence
Continuous variable (age) assessed via one way ANOVA

Table 6

Study Events Occurring up to 24 Months Following Transplantation by CMV Risk Group, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients 1990-1998

	Patients in each CMV Risk Group			Total	p-value*
	Low	Moderate	High		
Symptomatic CMV Infection					
Yes n(%)	0	25 (4.9)	28 (26.9)	53 (6.2)	<.001
No n(%)	247 (100)	482 (95.1)	76 (73.1)	805 (93.8)	
Acute Rejection					
Yes n(%)	112 (47.0)	204 (42.2)	41 (43.3)	357 (43.7)	.336
No n(%)	135 (53.0)	303 (57.8)	63 (56.6)	501 (56.3)	

*Discrete variables assessed via chi-square test of independence

Table 7

Characteristics of Renal Transplant Recipients by Gancyclovir Prophylaxis Occurring up to 24 Months Following Transplantation OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients 1990-1998

	Gancyclovir		No Gancyclovir		p-value
Gender n(%)					
Male	47	(50.5)	429	(56.1)	.866
Female	46	(49.5)	336	(43.9)	
Age					
Mean (SD)	43.56	(12.3)	46.02	(13.5)	.363
Panel Reactive Antigen					
High	13	(14.0)	54	(7.1)	.019
Low	80	(86.0)	711	(92.9)	
Diabetes n(%)					
Yes	19	(20.4)	205	(26.8)	.187
No	74	(79.6)	560	(73.2)	
Antilymphocytic Immunosuppression n(%)					
Yes	80	(86.0)	668	(87.3)	.724
No	13	(14.0)	97	(12.7)	
Donor n(%)					
Cadaveric	61	(65.6)	553	(72.3)	.176
Living	32	(34.4)	212	(27.7)	

*Discrete variables assessed via chi-square test of independence
Continuous variable (age) assessed via one way ANOVA

Table 8

Study Events Occurring up to 24 Months Following Transplantation by Gancyclovir Prophylaxis, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients 1990-1998

	Gancyclovir		No Gancyclovir		p-value
Symptomatic CMV Infection n(%)					
Yes	9	(9.7)	44	(5.6)	.138
No	84	(90.3)	721	(94.2)	
Acute Rejection n(%)					
Yes	8	(8.6)	349	(45.6)	<.001
No	85	(91.4)	416	(54.4)	

*Discrete variables assessed via chi-square test of independence

Table 9

Cox Proportionate Hazards Univariate Models Evaluating the Effect of Variables on Symptomatic CMV Infection, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients 1990-1998

Variable	Beta	p-value	Relative Risk	Relative Risk 95%CI	
Panel Reactive Antigen High Low	.467	.330	1.59 1.00	.62	4.07
Diabetes Yes No	.283	.427	1.33 1.00	.66	2.67
Antilymphocytic immunosuppression Yes No	.377	.348	1.46 1.00	.66	3.20
Age at Transplantation	.010	.389	1.01	.99	1.03
Donor Cadaveric Living Related	-.374	.235	.69 1.00	.37	1.27
Gancyclovir Prophylaxis Yes No	.538	.187	1.71 1.00	.77	3.81
CMV risk High Low/Moderate	2.320	<.001	10.17 1.00	5.55	18.64
Acute Rejection Yes No	.855	.004	2.35 1.00	1.31	4.21

Table 10

Cox Proportionate Hazards Final Multivariate Model Evaluating the Effect of Variables on Symptomatic CMV Infection, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients, 1990-1998

Variable	Beta	Chi-square	p-value	Relative risk	Relative Risk 95% CI	
Complete Model		104.221	<.001			
Acute Rejection Yes No	.642		.020	1.90 1.00	1.12	3.20
CMV risk group High Low/Moderate	2.270		<.001	9.68 1.00	5.61	16.64
Gancyclovir Prophylaxis Yes No	.472		.198	1.65 1.00	.56	3.92

Figure 1

Time to Symptomatic CMV Infection, Cox Proportionate Hazards Final Multivariate Model, Stratified by Gancyclovir Prophylaxis
OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients, 1990-1998

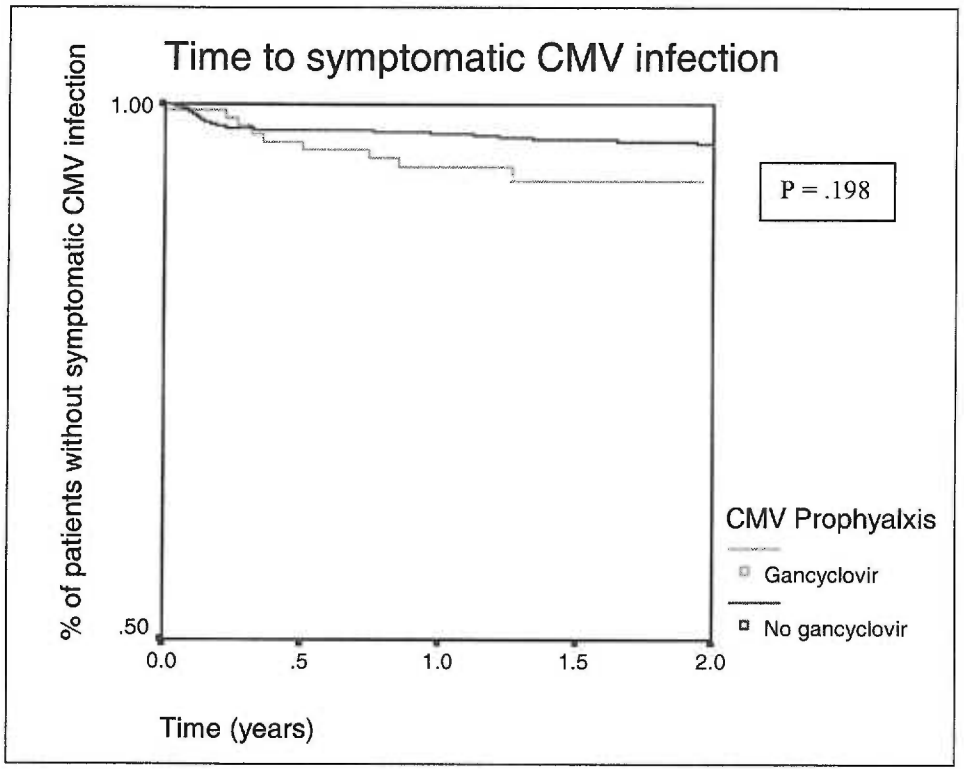


Table 11

Characteristics of Renal Transplant Recipients Following Transplantation Stratified by Matching Status, OHSU Renal Transplant Database: 858 Adult Kidney (only) Cadaveric Transplant Recipients, 1990-1998

	Matched	Not Matched	p-value
Gender n(%)			
Male	32 (52.5)	273 (49.4)	.687
Female	29 (47.5)	280 (50.6)	
Age			
Mean (SD)	45.0 (0.51)	46.5 (1.55)	.732
Panel Reactive Antigen			
High	8 (13.1)	40 (7.2)	.104
Low	53 (86.9)	513 (92.8)	
Diabetes n(%)			
Yes	14 (22.9)	162 (29.3)	.298
No	47 (77.0)	391 (70.7)	
Antilymphocytic Immunosuppression n(%)			
Yes	53 (86.9)	512 (92.6)	.119
No	8 (13.1)	41 (7.4)	
Gancyclovir prophylaxis n(%)			
Yes	41 (67.2)	20 (3.6)	<.001
No	20 (32.8)	533 (96.4)	
CMV Risk Group			
High	3 (4.9)	51 (9.2)	.260
Low/Moderate	58 (95.1)	502 (90.8)	

*Discrete variables assessed via chi-square test of homogeneity
Continuous variable (age) assessed via one way ANOVA

Table 12

Study Events Occurring up to 24 months Following Transplantation Stratified by Matching Status, OHSU Renal Transplant Database: 858 Adult Kidney (only) Cadaveric Transplant Recipients, 1990-1998

	Matched	Not Matched	p-value
Symptomatic CMV Infection n(%)			
Yes	3 (4.9)	25 (4.5)	.888
No	58 (95.1)	528 (95.5)	
Rejection n(%)			
Yes	1 (1.6)	275 (49.7)	< .001
No	60 (98.4)	278 (50.3)	

*Discrete variables assessed via chi-square test of homogeneity

Figure 2

Percentage of Symptomatic CMV Infections, Grouped by CMV Matching Status and Stratified by CMV Serological Risk Group, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients, 1990-1998

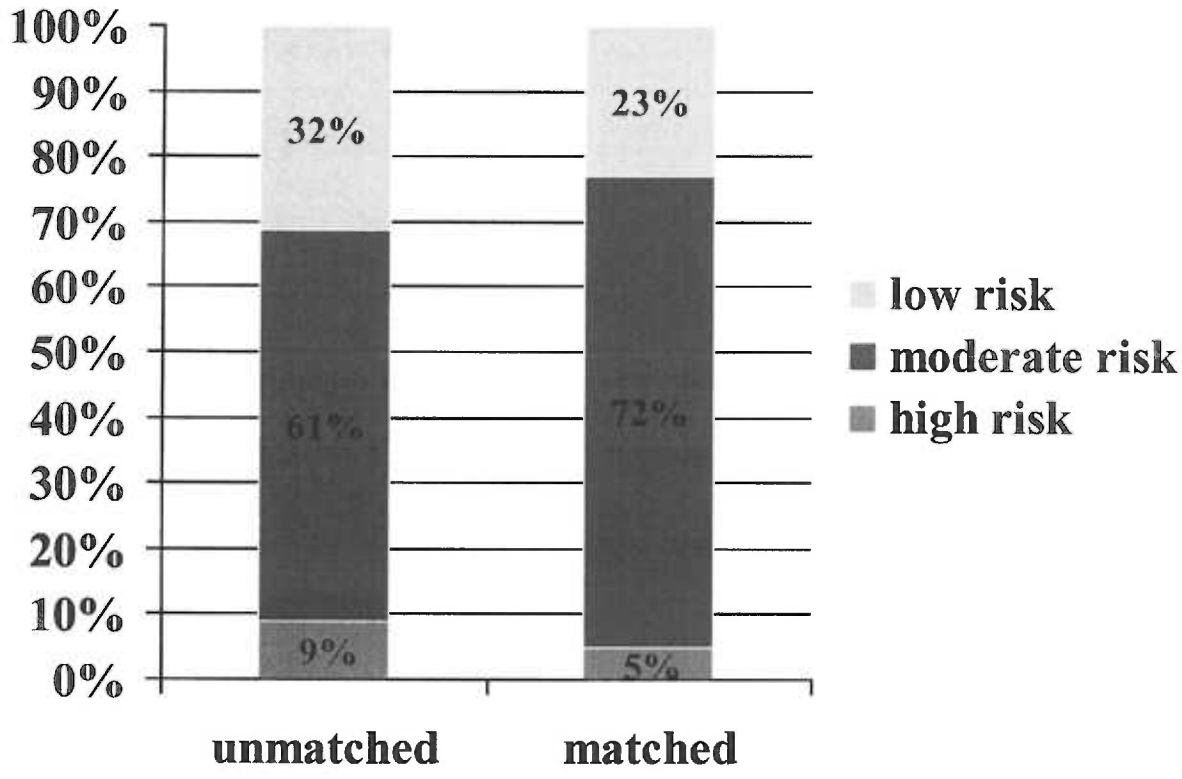


Table 13

Cox Proportionate Hazards Univariate Models Evaluating the Effect of Variables on Acute Rejection, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients, 1990-1998

Variable	Beta	p-value	Relative Risk	Relative Risk 95%CI	
Panel Reactive Antigen High Low	.333	.074	1.39 1.00	.97	2.01
Diabetes Yes No	- .034	.781	.97 1.00	.76	1.23
Antilymphocytic immunosuppression Yes No	.049	.787	1.05 1.00	.74	1.50
Age at Transplantation	- .014	.004	.99	.98	.99
Donor Cadaveric Living	.210	.345	1.23 1.00	.96	1.59
CMV risk group High Low/Moderate	- .332	.069	.72 1.00	.50	1.03
Gancyclovir Prophylaxis Yes No	-1.952	<.001	.14 1.00	.07	.29
Symptomatic CMV Infection Yes No	.711	.001	2.04 1.00	1.35	3.07

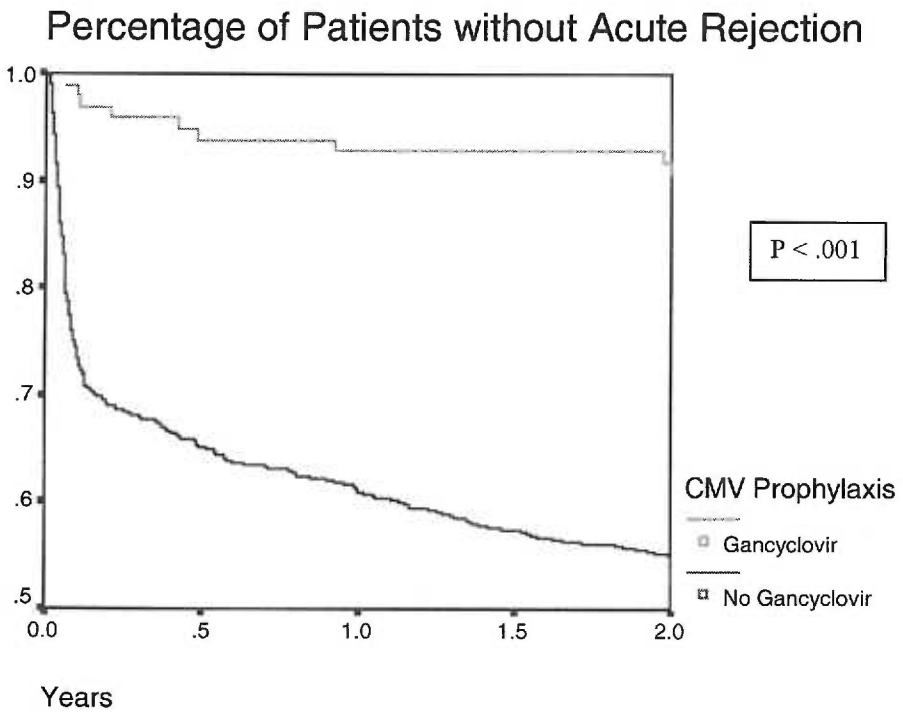
Table 14

Cox Proportionate Hazards Final Multivariate Model Evaluating the Effect of Variables on Acute Rejection, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients, 1990-1998

Variable	Beta	Chi-square	p-value	Relative Risk	Relative Risk 95% CI	
Complete Model		58.816	<.001			
Panel Reactive Antigen High Low	.342		.066	1.41 1.00	.98	2.03
Age at Transplantation	- .012		.007	.99	.98	.99
Gancyclovir Prophylaxis Yes No	-1.954		<.001	.14 1.00	.07	.29
CMV risk group High Low/Moderate	- .347		.057	.71 1.00	.50	1.00
Symptomatic CMV Infection Yes No	.684		.001	1.98 1.00	1.32	2.98

Figure 3

Time to First Acute Rejection, Cox Proportionate Hazards Final Multivariate Model, Stratified by Gancyclovir Prophylaxis, OHSU Renal Transplant Database: 858 Adult Kidney (only) Transplant Recipients, 1990-1998



Discussion

The Effect of Gancyclovir on Symptomatic CMV Infection

Conclusions

Patients treated with gancyclovir are less likely to develop symptomatic CMV infections during the first month following transplantation than those not treated with gancyclovir, but subsequently are as, or more, likely to develop symptomatic CMV infections. Variables associated with CMV infection include high-risk CMV group and acute rejection. Variables not associated with symptomatic CMV infection include antilymphocytic immunosuppression, cadaveric donor, high panel reactive antigen, diabetes and age at transplantation.

Discussion

This study demonstrated that the use of gancyclovir decreases the incidence of symptomatic CMV infections during the period in which the gancyclovir was administered but shortly thereafter the incidence increased, and by the end of the second year following transplantation, those treated with gancyclovir had an insignificantly greater number of infections than those not treated. This is consistent with the theory that gancyclovir prevents infection only during the period of time in which it is given.

A Cox proportionate hazards model created to examine the impact of variables on the development of symptomatic CMV infections included acute rejection (relative risk = 1.9, $p = .02$) and CMV high-risk group (relative risk 9.7, $p < .001$). CMV risk groups have been identified in previous studies as being closely correlated with risk of symptomatic CMV infection.[2,3] In a similar fashion acute rejection has been associated with CMV infection[4], though it remains unclear whether the CMV infection precedes

acute rejection or an episode of acute rejection precedes CMV infection. Additionally, patients who suffer an episode of acute rejection are often treated with antilymphocytic therapy, exposing them to an added risk factor for CMV infection.

Variables in the Cox proportionate hazards model not significantly associated with CMV infection included the presence of diabetes and age at transplantation, neither of which has been associated with symptomatic CMV infection in other studies. Panel reactive antigen and cadaveric donation have not been associated with increased rates of CMV in prior studies. Many studies have found increased rates of symptomatic CMV infection among patients treated with antilymphocytic therapy[5,6]. This study found no such association. A potential explanation may be the short post-transplant follow up periods in those studies. The longer transplant follow-up period in this study demonstrated a dissipation of the benefits of gancyclovir. In a similar fashion, the negative effects of antilymphocytic therapy may be ameliorated by longer follow-up periods. This possibility could be assessed by restricting the observation period in the present study to only several months, but that was outside the scope of this study.

Support for the use of gancyclovir prophylaxis has been based on the premise that gancyclovir decreases symptomatic CMV infections, a premise supported by studies with relatively short-term follow-up. In this study, with a longer follow-up period, gancyclovir prophylaxis had no long term positive impact on symptomatic CMV infections. The results support the hypothesis that gancyclovir prophylaxis decreases the risk of symptomatic CMV infections only during and perhaps immediately following the prophylactic period. This suggests that current use of gancyclovir prophylaxis to decrease symptomatic CMV infections should be reexamined.

Studies comparing gancyclovir prophylaxis with placebo or acyclovir prophylaxis have been limited by short post-transplant follow-up periods and longer (three-month) prophylaxis periods. For example, a randomized trial of comparing acyclovir prophylaxis and gancyclovir prophylaxis by Flechner et.al. 1998, found a significant difference in rates of CMV seroconversion between the two groups by the conclusion of the study. Patients received prophylaxis for 3 months and post-transplant follow-up lasted only six months allowing only three unprotected months during which gancyclovir treated patients could seroconvert. The lack of longer post-transplant follow-up limited findings of increased symptomatic CMV infections in gancyclovir treated patients.[1] The goal of this study was to examine the effects of gancyclovir prophylaxis beyond the period of prophylaxis (in this study the subsequent 23 months).

Limitations

This study suggests that gancyclovir may not be a particularly effective tool in preventing symptomatic CMV infections. As this study is a cohort study, it is limited by potential unrecognized confounders. In addition, one month of gancyclovir prophylaxis may not be a long enough period to adequately ensure the benefits of prophylaxis have been incurred.

The effect of unknown confounders may be particularly relevant when considering changes that have taken place throughout the period of this study with respect to time. Early in the study period patients were unlikely to receive gancyclovir, as it was not yet widely used. As the study period progressed into the later 1990's the use of gancyclovir became more and more prevalent. In addition, other changes that occurred over the period of study include changes in immunosuppressive protocols, surgical techniques and

donor demographics. In comparing patients given gancyclovir prophylaxis to those not given gancyclovir prophylaxis, these time related confounders might have played a role, especially since the use of gancyclovir increased between 1990 and 1998.

The two variables associated with increased risk of CMV infections were high risk group and acute rejection. Since these variables were included in the Cox proportionate hazards model, their impact on the observed effect was controlled. Other unknown confounders, such as changes in donor demographics were not included in the model and thus may have affected the outcome of the study. For example, antilymphocytic immunosuppressive protocols may not be more frequently employed than they were a decade ago, but the specific medications have changed. If the newer antilymphocytic induction protocols increase the risk of CMV, this may offset an unappreciated decrease provided by gancyclovir. Likewise changes in treatment of acute rejection episodes may increase the risk for symptomatic CMV infections. Such changes might explain the difference in outcomes between this study and those with shorter follow-up periods. As episodes of acute rejection may occur over many months following transplantation, more and more patients would be ultimately exposed to rejection treatment, which (assuming it increased the risk of symptomatic CMV infection) would gradually decrease the beneficial effects of gancyclovir. Studies with short term follow-up would find the benefit of the gancyclovir prophylaxis, while longer follow-up would see such a benefit decrease.

Clinically relevant questions not addressed by this study include:

1) Does the length of the prophylactic period (one vs. two or three months) affect the impact of gancyclovir prophylaxis on symptomatic CMV infections?

2) Does the short-term decrease in symptomatic CMV infections have secondary benefit (i.e. decreased mortality)?

These questions will require further investigation.

Future Directions

Before suggesting that gancyclovir be given to every renal transplant recipient, it seems reasonable to attempt a randomized controlled trial among patients who would not otherwise receive it, to further establish the benefit of decreasing in acute rejection. A randomized trial in patients expected to receive gancyclovir may be appropriate as well, in order to establish whether it decreases symptomatic CMV disease beyond six months. Finally, studies considering the length of time (one or three months) gancyclovir prophylaxis is administered should be conducted.

The Effect of CMV IgG Matching on Symptomatic CMV Infections

Conclusions

CMV IgG matching did not result in significantly decrease the development of symptomatic CMV infections when differences in gancyclovir prophylaxis, distribution of CMV positive cadaveric kidneys and acute rejection are considered. This study suggests that whatever benefit may be derived from CMV matching can be effectively nullified in a population by changes in the availability of CMV negative kidneys.

Discussion

Little has been published regarding the potential utility of a CMV matching program in a renal transplant program. More importantly, there is no published evidence that a CMV matching program actually decreases the presence of symptomatic CMV infections in a population of renal transplant recipients. Thus, a goal of this study was to verify and

quantify a reduction in overall symptomatic CMV infections due to CMV matching. The results suggest that while a reduction in symptomatic CMV infections occurred, it was relatively small and largely negated by the availability of CMV negative cadaveric kidneys.

When the initial chi square statistic was calculated comparing CMV infections in matched and unmatched patient groups, no significant difference was observed. The logistic regression model identified acute rejection (relative risk .375, $p = .028$) and CMV high risk (relative risk 8.797, $p < .000$) as significant variables. Even when placed in the logistic regression model with these variables, matching still failed to achieve significance ($p = .242$), though the relative risk (.437) does suggest that matching may decrease the risk for CMV infection.

It seems intuitive that by increasing the number of patients at low risk for CMV and by decreasing the number of high risk patients, the overall rate of CMV infection would be decreased. This does not, however, take into consideration the difference in gancyclovir use between risk groups or changes in the quantity of available CMV negative kidneys. It is possible that, because the redistribution of available cadaveric kidneys is reduced over time, and matching is also time related, the lack of a significant difference in CMV infection rates was affected by fewer CMV negative kidneys.

When the number of patients in the CMV low risk group increases, one would expect a decreased use of gancyclovir. This was not the case in this study. More patients in the matched group received gancyclovir than those in the unmatched group (67.2% vs. 3.6%, $p < .001$). The large percentage of patients in this study receiving gancyclovir may have affected the resulting outcome, as evidenced by the change in results from the chi-square

test ($p = .888$) to the logistic regression model ($p = .242$), but neither result was significant. Thus, the fact that more patients in the matched group received gancyclovir prophylaxis than in the unmatched group may have minimized a significant difference in CMV infection rates provided by matching.

Reasons for the difference in gancyclovir use are unclear, though it should be noted that guidelines for the use of gancyclovir for CMV prophylaxis were published[9] shortly following the start of the matching program at OHSU. If gancyclovir was given in the manner proposed by the guidelines, more patients in the matched cohort would have received the drug, resulting in the observed difference in gancyclovir prophylaxis between the matched and unmatched cohorts. Earlier results from this study, however, suggest that the benefit of gancyclovir prophylaxis for symptomatic CMV infection is limited to a short period of time following transplantation. If this finding is correct, there should be no observable benefit of gancyclovir prophylaxis in the matched group.

CMV matching is applied only to cadaveric transplants and is therefore influenced by the availability of CMV positive and CMV negative kidneys. The lack of a significant difference in symptomatic CMV infections found in this study occurred despite a (4.3%) decrease in the percentage of patients with high risk in cadaveric transplant recipients (9.2% to 4.9%). Notably, however, there was also a sizable (9%) difference in low risk cadaveric transplants during the same period (32% to 23%) as noted in Figure 2. The combination of these factors (decreased high risk, decreased low risk) is explained by a decrease in the proportion of CMV negative kidneys (49.7% receiving unmatched kidneys vs. 40.0% receiving matched kidneys). Thus, the lack of significant change in

the overall proportion of symptomatic CMV disease cases is likely to be the result of fewer CMV negative kidneys in the matched cohort.

Limitations

Comparisons of matched and unmatched patients may have been affected by time related confounders. Since matching occurred at a later time, changes in protocols or techniques that changed from the unmatched period to the matched period may have either increased or decreased differences in CMV infection rates.

The utility of CMV matching is drawn into question by the findings of this study. Despite it's intuitive merits, the availability of CMV negative kidneys seems more important to optimal outcomes. Programs aimed at increasing the number of kidneys from young donors (for example by distributing donor cards with driver's license tests) who are less likely to be CMV positive may be more likely to provide a decrease in symptomatic CMV infections in transplant populations.

Future Directions

The goal of CMV matching (and the reason it was implemented at OHSU) is to decrease the number of patients at high risk for CMV infection, and increase the number of low risk patients, resulting in an overall decrease in symptomatic CMV infections. The results of this study suggest that the distribution of CMV positive and negative kidneys may be more relevant in determining the likelihood that patients develop symptomatic CMV infections than the application of a matching program. To estimate the impact of this change, the proportion of symptomatic CMV infections in each CMV risk group can be used to estimate the potential impact of an increase in CMV negative

kidneys. Applying this information reveals that a 5% percent increase in proportion of CMV negative kidneys would yield a 17% decrease in symptomatic CMV infections.

Before continuing the matching program, more study of the effects of matching on recipient waiting times, increased moderate risk group patients and outcomes should be considered. A potential effect of implementing a matching program concerns the impact not only on the transplant population, but on each individual as well. CMV negative recipients may benefit as individuals from a matching program by receiving CMV negative kidneys. A matching program may prove detrimental, however, if there were a substantial increase in waiting times due to a paucity of available CMV negative kidneys. CMV positive recipients could potentially benefit from a matching program if the proportion of CMV positive kidneys is larger than the proportion of CMV positive recipients. This scenario would decrease waiting times for CMV positive recipients. Such a positive benefit could be outweighed by the potentially negative impact of receiving a CMV positive kidney as opposed to a CMV negative kidney. The results of this study do not imply that matching does or does not benefit an individual patient. Clearly, CMV negative recipients are less likely to develop a symptomatic CMV infection if they receive a CMV negative kidney. While this study examines the population-wide effect of a matching program, further studies regarding the patient-specific effects of matching should be undertaken.

The Effect of Gancyclovir Prophylaxis on Acute Rejection

Conclusions

Patients treated with gancyclovir are less likely to develop acute rejection during the first month following transplantation. The subsequent difference continues to increase

over the ensuing two years. Variables associated with acute rejection included age at transplantation (inversely correlated), CMV infection and panel reactive antigen. Variables not associated with acute rejection include CMV risk group, diabetes and antilymphocytic immunosuppression.

Discussion

There is little literature available on the potential secondary benefits of gancyclovir prophylaxis. The finding that gancyclovir may decrease acute rejections has not been previously noted, though the utility of gancyclovir in treating acute rejection has been considered. In one study, 21 patients who experienced late-acute rejections were given gancyclovir instead of the usual anti-rejection protocols[8]. Seventeen of the 21 patients improved.

If gancyclovir prophylaxis decreases symptomatic CMV infections (as previously assumed) and if symptomatic CMV infections predispose renal transplant recipients to acute rejection then gancyclovir prophylaxis should decrease acute rejections. This hypothesis is partially supported by the results of this study. Gancyclovir prophylaxis did decrease acute rejections, as expected. It did this, however, without decreasing symptomatic CMV infections.

This study demonstrated that the use of gancyclovir decreases the incidence of acute rejection during the period in which the gancyclovir was administered. The proportion of recipients free from acute rejection following this period continued to decrease at a slower rate among those treated with gancyclovir and those not treated.

A Cox proportionate hazards model constructed to assess the impact of other variables on acute rejection revealed the significance of the CMV high-risk group, age at

transplantation and symptomatic CMV infections. Patients in the CMV high risk group were 1.4 times less likely to develop acute rejection as those in the low risk group. The counter-intuitive finding may be explained by a larger proportion of patients in the high risk group receiving gancyclovir, thus decreasing risk of acute rejection. It suggests that gancyclovir may be more protective against acute rejection than is the CMV low risk status. Older patients were less likely to develop episodes of acute rejection, possibly owing to less active immune systems. Age at transplantation has been associated with acute rejection in some studies and not in others.[9,10]

Variables not significantly associated with acute rejection included presence of diabetes, high panel reactive antigen and cadaveric donation. Panel reactive antigen has been associated with increased rates of CMV in prior studies.[11] It was nearly significant in this study, and thus was included in the analysis. Cadaveric donation and diabetes have not previously been associated with acute rejection.[12]

The results of this study suggest a significant long-term reduction in episodes of acute rejection among patients given gancyclovir prophylaxis. This seems somewhat counterintuitive when considering that in this study, those receiving gancyclovir experienced no decrease in the number of symptomatic CMV infections, which have been implicated in predisposing patients to acute rejection. There are two potential explanations for this discrepancy: 1) Gancyclovir has intrinsic immunosuppressive properties that prevent acute rejection. 2) Gancyclovir prevents asymptomatic CMV infections, which in turn predispose patients to acute rejection. Neither of these explanations was examined in this study, and no literature exists regarding the direct effect of gancyclovir on acute rejection.

Further research into the relationship between gancyclovir prophylaxis and acute rejection seems warranted given the enormous potential benefit suggested by the results of this study.

Limitations

The finding in this study suggests that gancyclovir may not be a particularly effective tool in protecting patients from symptomatic CMV infections, but may be extremely potent in decreasing acute rejection. As this study is a cohort study, it is limited by potential unrecognized confounders. In addition, one month of gancyclovir prophylaxis may not be a long enough period to adequately ensure the benefits of CMV prophylaxis have been incurred.

The effect of unknown confounders may be particularly relevant when considering changes that have taken place throughout the period of this study with respect to time. Early in the study period patients were unlikely to receive gancyclovir, as it was not yet widely used. As the study period progressed into the later 1990's the use of gancyclovir became more and more prevalent. In addition, other changes that occurred over the period of study include changes in immunosuppressive protocols, surgical techniques or donor demographics. In comparing patients given gancyclovir prophylaxis to those not given gancyclovir prophylaxis, these time-related confounders might have played a role, especially since the use of gancyclovir increased between 1990 and 1998.

If a time-related confounder were to have altered the outcome of this study it would have to have a large effect on the likelihood of developing an acute rejection, as patients in this study who did not receive gancyclovir were over seven times more likely to develop an acute rejection episode. In addition, it would have to be present over the two

year period following the study, since the beneficial effect of gancyclovir appears to have been present over the entire two years following transplantation. It seems unlikely that a confounder with such a sizable, lengthy impact would go unnoticed.

Future Directions

Before suggesting that gancyclovir be given to every renal transplant recipient, it seems reasonable to attempt a randomized controlled trial in patients who would not otherwise receive it, to further establish the benefit in decreasing in acute rejection. A randomized trial in patients expected to receive gancyclovir may be appropriate as well, in order to establish whether it decreases symptomatic CMV disease beyond six months. Finally, studies considering the length of time (one or three months) gancyclovir prophylaxis is administered should be considered.

References

1. Flechner SM, Avery RK, Fisher R, Mastroianni BA, et.al.. A Randomized Prospective Controlled Trial of Oral Acyclovir Versus Oral Gancyclovir For Cytomegalovirus Prophylaxis in High-Risk Kidney Transplant Recipients. Transplantation 66:1682-1688. 1998.

2. Hibberd PL, Snydman DR. Cytomegalovirus Infection in Organ Transplant Recipients. Infectious Disease Clinics of North America. 9:863-873. 1995.

3. Rubin RH. Impact of Cytomegalovirus Infection on Organ Transplant Recipients. Rev Infect Dis 12(Supp 7):S754-S766. 1990.

4. Bouedjoro-Camus MC, Novella JL, Toupance O, et.al.. Cytomegalovirus infection, a risk factor for acute rejection in renal transplant recipients. A Case Controlled Study. Presse Medicale. 28:619-624. 1999.

5. Hibberd PL, Tolkoff-Rubin NE, Cosimi AB, et.al.. Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipients treated with OKT3. Transplantation. 53:68. 1992.

6. Singh N, Gayowski T, Wagener M, et.al.. Infectious complications in liver transplant recipients on tacrolimus: A prospective analysis of 99 consecutive liver transplants. Transplantation. 58:774. 1997.

7. Jassal SV, Roscoe JM, Zaltzman JS, et.al.. Clinical Practice Guidelines: Prevention of Cytomegalovirus Disease after Renal Transplantation. JASN. 9:1697-1708. 1998.
8. Reinke P, Fietze E, Ode-Hakim S, et.al.. Late-acute allograft rejection and symptomless cytomegalovirus infection. Lancet. 345:1737-8. 1994.

9. Kouli F, Morrell CH, Ratner LE, Kraus ES. Impact of donor/recipient traits independent of rejection on long-term renal function. Am J Kidney Dis 37:356-65. 2001.

10. Prabhu R, John GT, Shankar V, et.al.. Pre-transplant risk factors for renal allograft dysfunction at one year in Indian patients. Natl Med J India 14:18-21. 2001.

11. Barama A, Oza U, Panek R, et.al.. Effect of recipient sensitization (peak PRA) on graft outcome in haploidentical living related kidney transplants. Clin Transplant 14:212-7. 2000.

12. Revanur VK, Jardine AG, Kingsmore DB, et.al.. Influence of diabetes mellitus on patient and graft survival in recipients of kidney transplantation. Clin Transplant 15:89-94. 2001.