Prevention and treatment of cytomegalovirus infection in transplant recipients

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JK PREIKSAITIS. **Prevention and treatment of cytomegalovirus infection in transplant recipients. Can J Infect Dis 1993;4(Suppl C):43C-50C.** Over the past decade, significant progress has been made in the understanding of the molecular biology of cytomegalovirus (CMV) and the pathogenesis of CMV infection and disease. The introduction of antiviral agents with efficacy against CMV, coupled with rapid diagnostic techniques in the laboratory, have resulted in the design of a number of regimens to prevent, modify and treat CMV infections in transplant recipients. Strategies for preventing CMV infection, including donor-recipient matching, the use of CMV 'safe' cellular blood products, passive and active immunization, and prophylactic antiviral drugs are discussed. Clinical trials of antiviral drugs alone, or in combination with immunoglobulin for the treatment of CMV disease are reviewed.

Key Words: *Bone marrow transplantation, Cytomegalovirus, Organ transplantation*

Prévention et traitement de l'infection à cytomégalovirus chez les receveurs de transplantation

RÉSUMÉ: Au cours de la décennie écoulée, de grands progrès ont été accomplis dans la compréhension de la biologie moléculaire du cytomégalovirus (CMV), de la pathogenèse de l'infection à CMV et de la maladie qui en résulte. L'introduction d'agents antiviraux efficaces contre le CMV, doublée de techniques diagnostiques rapides en laboratoire ont permis la conception de certains schémas aptes à prévenir, modifier et traiter les infections à CMV chez les receveurs de transplantation. Les stratégies prophylactiques contre l'infection à CMV, y compris la correspondance donneur-receveur, l'utilisation de produits sanguins cellulaires dépourvus de CMV, l'immunisation passive et active et les médicaments antiviraux prophylactiques sont présentés. Les essais cliniques portant sur des médicaments anti-viraux seuls ou en combinaison avec l'immunoglobuline pour le traitement de la maladie à CMV sont passés en revue également.

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CYTOMEGALOVIRUS (CMV) INFECTION IS THE MOST COMMON infectious complication seen after solid organ and bone marrow transplantation. Acute CMV infection has direct consequences to the transplant recipient, often leading to significant morbidity and even mortality. Common symptoms include: fever; bone marrow suppression leading to leukopenia and thrombocytopenia; gastrointestinal disease including ulceration, perforation and hemorrhage; hepatitis; and pneumonitis (1). Encephalitis is seen less commonly and chorioretinitis is a relatively infrequent and late complication of CMV infection in this setting. As well as direct effects, CMV has indirect effects on the host (1). The virus is immunosuppressive and predisposes the host to superinfection with bacterial, fungal and parasitic pathogens. Whether CMV infection precipitates acute graft rejection remains controversial. CMV also has been implicated as a contributing factor to the sequelae leading to late graft failure, which include graft atherosclerosis in the heart transplant recipient, vanishing bile duct syndrome in the liver transplant recipient and bronchiolitis obliterans in the lung transplant recipient.

There are several potential sources of CMV infection in the transplant recipient (1). Patients seropositive prior to transplantation may undergo reactivation of endogenous virus. The transfusion of cellular blood products provides an additional potential source of infection. The most important source of CMV infection in solid organ and bone marrow transplantation is the seropositive donor organ or bone marrow. Recent evidence in renal and heart allograft recipients suggests that in CMV seropositive transplant recipients, reinfection by CMV strains transmitted by the donor organ frequently occurs (2).

Several factors have been found to influence the severity of CMV disease in allograft recipients (1). The type of allograft received appears to be important. For example, renal allograft recipients appear to experience less CMV-associated morbidity than heart, lung and liver transplant recipients. This may be an indirect reflection of the aggressiveness of immunosuppression required to prevent graft rejection. However, there appears to be a predilection for CMV to appear first in the transplanted organ and result in major morbidity at this site. For example, liver transplant recipients are predisposed to CMV hepatitis, and lung transplant recipients to CMV pneumonitis. Bone marrow transplant recipients appear to be at significantly higher risk of CMV-associated interstitial pneumonitis, and the risk of its occurrence and the severity of disease have been linked to the presence and severity of graft versus host disease in this subgroup of patients (3). In general, patients who are CMV seronegative prior to transplant and experience a primary CMV infection, are at greater risk of CMV disease than those seropositive prior to transplant who experience CMV reactivation or reinfection (1). Although this remains somewhat controversial,

TABLE 1
Strategies for the prevention of cytomegalovirus disease

1. Matching of donor-recipient serostatus
2. Screening of cellular blood products
3. Vaccine
4. Passive immunotherapy
5. Prophylactic drugs:
    Interferon-alpha
    Acyclovir
    Foscarnet
    Ganciclovir
    Valine ester of acyclovir
6. Combination of passive immunotherapy plus antiviral drug
7. Pre-emptive therapy

the bulk of evidence suggests that in these seropositive patients, reinfection events are associated with more morbidity than endogenous reactivation of virus (1,2). The use of polyclonal or monoclonal (OKT3) antilymphocyte globulins have also been demonstrated to increase the risk of CMV disease in solid organ transplant recipients (1,4).

Over the past decade, significant progress has been made in our understanding of the molecular biology of CMV and the pathogenesis of CMV infection and disease. The introduction of antiviral agents with efficacy against CMV, coupled with rapid diagnostic techniques in the laboratory, have resulted in the design of a number of regimens to prevent, modify and treat CMV infections in transplant recipients. Many of the reports of the use of these regimens represent uncontrolled studies. The use of historical controls is particulary difficult in the transplant setting with its rapidly changing immunosuppressive protocols. Therefore this paper deals largely with interventions that have been studied using controlled trials.

PREVENTION OF CMV INFECTIONS
Some of the approaches that have been used for the prevention of CMV disease are listed in Table 1.

CMV infection is extremely common after transplantation and in most patients is asymptomatic. In choosing a strategy for the prevention of CMV disease, it is important to identify clearly, through epidemiological or laboratory parameters, the patients who are at highest risk of CMV-associated morbidity and to target this subgroup specifically for preventive strategies. The potential toxicity of the regimen proposed as well as the cost should be considered. One must also examine the logistics of the delivery of the preventive regimen. Since often the greatest portion of the risk period for CMV infection after transplantation is spent in an out-patient setting, oral agents would clearly be preferable to intravenously administered products.

Donor recipients – CMV matching: Because the source of CMV infection in most cases of primary CMV

TABLE 2
Transfusion-acquired cytomegalovirus infection in seronegative bone marrow transplant recipients

Study (reference)	Group	Number of patients	Number infected	Significance	Conclusions
Bowden et al (allogeneic) (7)	Control (standard blood)	28	8	P<0.007	CMV seronegative blood products significantly reduced the risk of CMV infection of seronegative but not seropositive marrows
	Study (CMV– red blood cells, platelets)	32	1		
Bowden et al (autologous/some allogeneic) (8)	Control (standard blood)	30	0	P<0.001	Leukocyte-depleted platelets and CMV-seronegative red blood cells are highly effective in preventing primary CMV infection
	Study (CMV– red blood cells, leukocyte-depleted platelets, centrifugation)	35	7		
Miller et al (allogeneic) (9)	Control (standard blood)	44	14	P<0.006	Confirms study of Bowden et al above. However, the use of seronegative blood products did not improve survival
	Study (CMV– red blood cells, platelets)	45	2		

CMV Cytomegalovirus

infection in solid organ transplant recipients is the CMV seropositive organ, it has been suggested that the use of CMV seropositive donors be avoided in CMV seronegative recipients. However, the shortage of suitable donor organs and the presence of critical illness in the recipient often makes this approach impractical in all but the largest transplant programs.

Use of CMV 'safe' cellular blood products: CMV is known to be transmitted by blood transfusion. Despite the fact that in Canada approximately 50% of blood products come from CMV seropositive donors, cellular blood products are a relatively infrequent source of CMV infection compared with the seropositive donor organ or bone marrow (5). CMV is believed to be transmitted in the latent form in the leukocyte fraction of cellular blood products and reactivated in the recipient. The use of CMV seronegative cellular blood products or processing techniques, such as the use of frozen de-glycerolized red blood cells, differential centrifugation of platelets and the use of the new generation leukocyte filters, will render these products CMV 'safe' (5). However, these procedures are associated with considerable cost. Although the use of CMV seronegative blood products for CMV seronegative recipients (R-) of CMV seronegative donor organs (D-) or bone marrow have been recommended by some authors (6), the efficacy of this approach has only been proven in bone marrow transplantation (7-9) (Table 2). In allogeneic and autologous bone marrow transplantation where the use of cellular blood products, particulary highly leukocyte-contaminated platelet units, is large, the use of CMV 'safe' blood significantly reduces the risk of CMV infection. Interestingly, Miller et al (9) found that this decreased risk of CMV infection was not associated with improved patient survival. It is not clear that these findings can be extrapolated to the solid organ transplant population.

Whether the use of CMV 'safe' blood products in R-D- kidney recipients would have any significant impact on CMV disease after renal transplantation is questionable (5). In the age of erythropoietin administration, kidney allograft recipients usually receive only small numbers of red cell units when transfused. In the more heavily transfused heart, lung and liver transplant recipient, the incidence of transfusion-acquired infection is also surprisingly low, although in the highly transfused liver transplant recipient, incidences as high as 20% in the D-R- subgroup have been reported (personal communication) (5). There is a clear need for controlled studies to determine the impact of the use of CMV 'safe' blood products in solid organ transplantation prior to recommending this as routine policy for D-R- transplant recipients.

Vaccine: Plotkin et al (10) have recently reported the results of a 10-year study of the effect of a live attenuated CMV Towne vaccine on CMV disease after renal transplantation. This was a double-blind, placebo controlled trial. They demonstrated that the vaccine was well-tolerated and safe. Although the vaccine did not prevent CMV infection, vaccination of CMV seronegative renal transplant recipients resulted in a reduction in the severity of CMV disease in this subgroup of patients. There are theoretical risks associated with using a live DNA virus vaccine, particulary in patient groups who are not immunocompetent because of their chronic disease state prior to transplant. The future of this vaccine will be somewhat dependent on how it compares in efficacy, cost and ease of administration with prophylactic regimens involving the use of immunoglobulin and antiviral agents.

Passive immunotherapy: In the early 1980s, the availability of intravenous immune globulin preparations and the lack of an antiviral drug with significant activity

TABLE 3
Controlled trials of immune globulin for cytomegalovirus prophylaxis

Study (reference)	Transplant	Globulin product (source)	Recipient CMV serological status (number of patients)	Comments
Winston et al (11)	Bone marrow	Immune globulin (Cutter Biological, California)	Positive (12) Negative (63)	Treatment group had less CMV disease (P=0.03), interstitial pneumonia (P=0.02) and GVHD (P=0.01)
Condie and O'Reilly (12)	Bone marrow	Hyperimmune globulin (Condie)	Positive (10) Negative (25)	Treatment group had less CMV infection (P=0.009), interstitial pneumonia (P=0.014) and mortality (P=0.014)
Meyers et al (13)	Bone marrow	Hyperimmune globulin (Massachusetts Biologic Laboratories, Massachusetts)	Negative (62)	In patients not receiving granulocyte transfusions, decreased CMV infection (P=0.03) in treatment group
Bowden et al (3)	Bone marrow	Hyperimmune globulin (Cutter Biological)	Negative (123)	Treatment group had less CMV excretion (P=0.04) and viremia (P=0.01), but no effect on CMV disease, hospitalization or patient survival
Snydman et al (14)	Renal	Hyperimmune globulin (Massachusetts Biologic Laboratories)	Negative (59)	Treatment group had significantly less CMV disease (P<0.01) fungal and parasitic superinfections (P<0.05) and leukopenia (P<0.01)
Steinmuller et al (15)	Renal	Immune globulin (Sandoz, New Jersey)	Positive (34)	Treatment group had significantly less CMV-associated fever (P=0.02) and complications (P=0.02)
Metselaar et al (16)	Renal*	Hyperimmune globulin (Cytotect, Dreieich, Germany)	Positive (23) Negative (11)	Treatment group had a decrease in viremia-associated death (P<0.05)
Saliba (17)	Liver	CMV hyperimmune globulin (French)	Negative (34)	Treatment reduced the incidence of CMV disease (P=0.01) in seronegtive recipients of seropositive donors

*CMV Cytomegalovirus; GVHD Graft-versus-host disease; *Treatment initiated with antirejection therapy*

against CMV, led to a number of clinical trials examining the role of passive antibody as prophylaxis for CMV disease after transplantation.

In transplant recipients, CMV disease occurs in the presence of high levels of neutralizing antibody (2). The effective anti-CMV component in immunoglobulin preparations is unknown. It is therefore impossible to standardize the product and accurately determine optimal dosing regimens. It is also not clear whether 'hyperimmune' CMV products defined using enzyme immunoassay or neutralizing titres are clearly superior to standard immunoglobulin. The majority of controlled studies using passive immunization have been carried out in the bone marrow transplant setting (Table 3). In these patients, the issue is further complicated by the observation that high dose intravenous immunoglobulin affects the incidence of graft versus host disease, presumably through its immunomodulating function. Since graft versus host disease is a known risk factor for severe CMV infection, specifically interstitial CMV pneumonitis, passive immunization in this setting may

be playing an indirect role in modifying CMV disease. Many of these studies included both seronegative and seropositive recipients who received marrows from both seronegative and seropositive donors. This makes data analysis difficult. The largest study, by Bowden et al (3), examined 123 seronegative recipients of seropositive donor marrows and found no effect of hyperimmune intravenous immunoglobulin on CMV disease, although a decrease in CMV excretion and viremia were observed. This study, however, showed no clear effect of immunoglobulin on graft-versus-host disease. The number of studies of the immunoglobulin prophylaxis in solid organ transplantation, particularly in extrarenal transplant recipients, is also limited. In seronegative recipients of seropositive donor kidneys, Snydman et al (14), found that prophylactic hyperimmune CMV globulin had a significant effect on CMV disease, fungal and parasitic superinfections, and leukopenia. However, the protective effect of the immunoglobulin was found to be attenuated by increased immunosuppression, specifically by the use of antilymphocyte globulins

TABLE 4
Controlled trials of antiviral drugs for cytomegalovirus prophylaxis

Study (reference)	Transplant	Drug	Dosage	Comments
Hirsch et al (19)	Renal (seropostitive)	Interferon-alpha	3×10^6 units preoperatively; 3 per week for 6 weeks, then 2 per week for 8 weeks	Treatment group had less CMV disease (P=0.03); opportunistic superinfections occurred only in patients given placebo
Meyers et al (20)	Allogeneic bone marrow (seropositive for both HSV and CMV)	Acyclovir (intravenous)	500 mg/m^2 every 8 h from preoperative day 5 to postoperative day 30	Treatment group had less CMV infection (P=0.0001), CMV disease (P=0.008) and improved survival (P=0.002)
Balfour et al (21)	Renal	Acyclovir (oral)	800 mg qid for 12 weeks	Treatment group had less CMV infection (P=0.01) and CMV disease (P=0.002); greatest prophylactic benefit observed in seronegative recipients who received a kidney from a seropositive donor
Merigan et al (25)	Cardiac	Ganciclovir	5 mg/kg every 12 h from days 1 to 14, then 6 mg/kg/day 5 times a week until day 28	Seropositive patients in the treatment group experienced less CMV disease (P<0.001); no effect seen in seronegative patients

CMV Cytomegalovirus; HSV Herpes simplex virus

for antirejection therapy (18). Since this is the patient group at greatest risk of serious CMV disease, the use of immunoglobulin alone for CMV prophylaxis probably represents a suboptimal strategy. The use of intravenous globulin preparations also has disadvantages in the form of high cost and the need for repetitive, lengthly intravenous infusions. The introduction of drugs active against CMV may replace the need for a passive immunization or result in its use in combination protocols.

Antiviral drugs (Table 4): Before the introduction of antiviral drugs specific for CMV infection, interferon-alpha was studied as a prophylactic agent for CMV infection in renal transplant recipients. In a group of seropositive renal transplant recipients, interferon-alpha was found to decrease the incidence of CMV disease and opportunistic superinfections (19). However, several episodes of acute vascular rejection associated with the use of interferon-alpha were later documented (1). Combined with the high cost of this product, this has largely eliminated it as a potential prophylactic agent in the transplant setting.

Acyclovir inhibits CMV replication in vitro although it does so at much higher concentrations than are required to suppress replication of herpes simplex virus or varicella zoster virus. Although it has not been shown to be effective in the treatment of established CMV disease, it appears to have some effect as a prophylactic agent. In a study using intravenous acyclovir administered to bone marrow transplant recipients for the first 30 days, Meyers et al (20) observed a significant decrease in CMV infection and disease. Balfour et al (21) found a similar decrease in CMV disease when renal allograft recipients received high dose oral acyclovir prophylactically. In this study, this effect was

only statistically significant in the seronegative recipient of a seropositive donor kidney. Surprisingly, this effect was observed in the presence of plasma levels lower than those required to inhibit CMV replication in vitro (22). New acyclovir derivatives which result in significantly higher drug levels in plasma when given orally are under study for CMV prophylaxis.

Ganciclovir (23) and foscarnet (24) are two antiviral agents which demonstrate significantly better inhibition of CMV replication in vitro than acyclovir. However, the bone marrow suppressive effect of ganciclovir and the nephrotoxicity of foscarnet has led to a reluctance to use these drugs routinely as prophylactic agents, particularly in bone marrow transplant recipients and in patients receiving cyclosporine, respectively. Ganciclovir prophylaxis has been studied in heart transplant recipients (25). A one-month course of prophylactic ganciclovir resulted in a reduced incidence of CMV disease in seropositive patients. In this study no effect was observed in seronegative recipients of seropositive donor hearts. A significant beneficial effect of ganciclovir prophylaxis on the incidence of CMV disease and pneumonitis in bone marrow transplant recipients was reported by Atkinson et al (26). However, this study used historical controls. In lung transplant recipients, two studies examining the use of prophylactic ganciclovir followed by oral acyclovir have reported contradictory findings with respect to efficacy (27,28). Foscarnet prophylaxis has been studied in a phase I and phase II trial in the bone marrow transplant setting (29). This initial study looks promising with respect to the efficacy of foscarnet on CMV disease. However, significant renal toxicity was observed when foscarnet was used in combination with amphotericin B. Both ganciclovir and foscarnet have a major disadvantage in

TABLE 5
The use of the 'pre-emptive strike' for the prophylaxis or early treatment of cytomegalovirus disease

Study (reference)	Patients	Design	Comments
Schmidt et al (31)	Bone marrow transplant recipients	Treatment with ganciclovir (5 mg/kg 12 h for two weeks, then 5 mg/kg/day 5 times a week to day 120) based on BAL culture positivity on day 35 (controlled randomized)	Decreased incidence of CMV pneumonitis ($P=0.01$)
Goddrich et al (32)	Bone marrow transplant recipients	Treatment with ganciclovir (5 mg/kg every 12 h for 1 week, then 5 mg/kg/day to day 100) based on positive surveillance cultures of throat swabs, urine, blood, BAL (controlled randomized)	Decreased incidence of CMV disease ($P<0.00001$) and improved survival ($P=0.041$)
Hibberd et al (4)	Renal transplant recipients	Treatment with ganciclovir (2 mg/kg/day) in conjunction with OKT3 rejection therapy (pilot study)	Decreased incidence of symptomatic CMV disease compared with historical controls

BAL Bronchoalveolar lavage; CMV Cytomegalovirus

TABLE 6
Treatment of cytomegalovirus pneumonia with ganciclovir and immunoglobulin in bone marrow transplant patients

Study (reference)	Survival of first episode (%)
Emanuel et al (33)	8 of 10 (80)
Reed et al (34)	13 of 25 (52)
Schmidt et al (35)	9 of 13 (69)
Ljungman et al (36)	15 of 49 (31)

their requirement for intravenous administration. There is a clear need for better anti-CMV drugs that can be administered orally for use in prophylactic regimens to prevent CMV disease.

'Pre-emptive strike': The observed toxicity of ganciclovir (23) and foscarnet (24) coupled with the observation that only a subset of transplant recipients are at significant risk for CMV disease, has lead to a strategy of intervention which lies somewhere in the spectrum between late prophylaxis and early treatment. This approach has been called the 'pre-emptive strike'. It is based on the use of antiviral therapy initiated in response to evidence of CMV infection such as positive CMV cultures during laboratory surveillance of patients or clinical parameters such as the use of antilymphocyte globulins for rejection therapy (30). This approach has been demonstrated to be extremely effective in bone marrow transplant recipients (Table 5) (31,32). Studies in solid organ transplantation are extremely limited. However, in a pilot study of renal transplant recipients, the use of ganciclovir in combination with OKT3 rejection therapy had a significant impact on CMV disease compared with historical controls (4). In this study, the dose of ganciclovir used was significantly lower than the usual therapeutic dose used to treat established disease. The presence of viremia has been identified as a risk factor for the development of a symptomatic CMV infection (30,32). The development of rapid diagnostic tests to detect and quantify viremia such as the direct antigenemia assay and polymerase chain reaction may allow simple and efficient monitoring of patients after transplant. This may allow identification of patients at high risk of CMV disease leading to a more selective use of the 'pre-emptive strike' approach.

TREATMENT OF CMV DISEASE

Over the past two decades, the acquired immunodeficiency syndrome (AIDS) epidemic and an increasing number of solid organ transplant recipients resulted in large numbers of immunocompromised patients with serious CMV disease. This led to the extensive use of ganciclovir and foscarnet on a compassionate plea basis, and the strong impression by many clinicians that treatment of CMV disease with these drugs resulted in significant benefit. Unfortunately, placebo controlled, double-blind protocols were never used to validate the anti-CMV efficacy of these agents in vivo. Ethical considerations will now likely prohibit these trials from being done. Much of the data regarding the efficacy of foscarnet and ganciclovir is therefore based on outcomes in treated patients compared with historical controls (23,24).

The most common forms of CMV disease include fever, pneumonitis, gastrointestinal disease and retinitis. The best evidence for the efficacy of antiviral therapy for the treatment of CMV disease is found in the bone marrow transplant setting. CMV pneumonitis is a serious complication of bone marrow transplantation resulting in an 85% mortality. The use of ganciclovir or immunoglobulin alone does not affect a patient's survival. However, the combination of ganciclovir and immunoglobulin therapy has been found to result in a significant improvement in survival (Table 6) (33-36). Ganciclovir alone is effective in limiting viral replication. The mechanism by which immunoglobulin has an additive beneficial effect is not known. There is an increasing body of evidence to suggest that CMV pneumonitis is an immunopathological disease and that immunoglobulin may be acting as an immunomodulator or through its effect on graft-versus-host disease.

Although both an antiviral drug and immunoglobulin appear to be required in the setting of CMV pneumonitis in bone marrow transplant and perhaps lung transplant recipients, it is not clear whether the immunoglobulin therapy is necessary for the treatment of pneumonitis in other solid organ transplant recipients.

Although there are large numbers of uncontrolled reports suggesting that ganciclovir may be of clinical benefit in the treatment of CMV gastrointestinal disease (23), controlled studies are limited. In a placebo controlled, randomized study of ganciclovir for the treatment of CMV gastroenteritis in bone marrow transplant recipients, it was found that although virus shedding was effectively terminated by antiviral therapy, there was no difference in either clinical symptoms or endoscopic appearance between the groups after treatment (37). Although there are no data in solid organ transplant recipients, the results of a recent placebo controlled trial of ganciclovir for CMV colitis in AIDS patients have been reported (38). The investigators found that ganciclovir treatment was associated with improved endoscopy scores, less extracolonic CMV disease and less weight loss. The efficacy of either foscarnet or ganciclovir for treatment of CMV gastrointestinal disease in solid organ transplant recipients remains unproven. There is no evidence to suggest that the use of adjunctive immunoglobulin therapy is beneficial.

Unlike AIDS patients, organ transplant recipients rarely develop CMV chorioretinitis. Although foscarnet

may have some advantages over ganciclovir in the treatment of CMV retinitis in AIDS, this may be due to the effect of foscarnet on human immunodeficiency virus infection rather than its direct effect on CMV replication. In the transplant setting, there is no evidence that foscarnet has any clear advantage over ganciclovir.

In the past when fever alone was the only symptom of CMV disease, treatment was usually not instituted. However, fever often results in significant patient morbidity, rehospitalization and extensive investigation. As experience with the use of ganciclovir and foscarnet increases, there has been a general trend among transplant physicians to institute antiviral therapy earlier in patients with symptomatic CMV infection with a view to preventing tissue invasive disease. Data to support the efficacy of this approach are lacking.

Although significant progress has been made, based on the evidence available, it is difficult to make definitive recommendations regarding the optimal regimens for either the prophylaxis or treatment of CMV disease. Much work remains to be done. There is a clear need for a better oral anti-CMV drug. The clinical usefulness of rapid diagnostic tests such as the quantitative direct antigenemia assay and polymerase chain reaction for the identification of patients at high risk of CMV disease should be examined. There is a need for further controlled studies comparing currently available regimens for both the prophylaxis and treatment of CMV disease.

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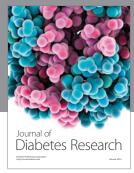
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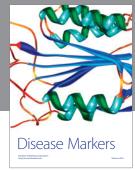28. Duncan SR, Paradis IL, Dauber JH, Yousem SA, Hardesty RL, Griffith BP. Ganciclovir prophylaxis for cytomegalovirus infections in pulmonary allograft recipients. Am Rev Respir Dis 1992;146:1213-5.

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