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Mini review

Immune globulin versus antivirals versus combination for prevention of cytomegalovirus disease in transplant recipients

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1. Immune globulin versus antivirals versus combination for prevention of cytomegalovirus disease

Cytomegalovirus (CMV) disease affects the outcome for all types of transplantation but the different types of transplants are associated with different risks for CMV disease and morbidity. Therefore, it is unlikely that one strategy would be appropriate for all patients Goodrich et al., 1994; Winston, 1995; Badas and Stoukides, 1996; Griffiths, 1997). Indeed, recent guidelines for management of CMV infection suggest approaches stratified according to the risk profiles of a given population (Hebart et al., 1997).

For the purpose of this review, I will compare the results of the clinical trials in four groups—bone marrow transplantation (BMT), renal transplantation, liver transplantation, and heart and lung transplantation. Most weight is given to evidence from randomized controlled trials (RCT) with the evidence from uncontrolled prospective and retrospective trials considered for supportive evidence. One of the limitations in comparing the clinical trials for CMV prophylaxis is the change over the last decade in diagnostic techniques available for detection of CMV, from traditional cell culture through to polymerase chain reaction (PCR) and other molecular techniques (Boeckh et al., 1996b; Einsele et al., 1991). Thus, CMV infection and CMV disease may have been underestimated in earlier trials compared with the more recent trials. Since there are few trials using foscarnet or other anti-viral agents as an antiviral prophylactic agent, this review focuses on acyclovir (ACV) and ganciclovir (GCV) as antiviral prophylactic agents.

Cytomegalovirus infection is associated with many complications post-transplant, such as fungal infections (Collins et al., 1994) graft rejection Richardson et al., 1981 and graft dysfunction (Grattan et al., 1989). The effect of antiviral

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agents or immunoglobulins on these associated complications is beyond the scope of this review.

The strategies that have been used to prevent CMV disease include use of CMV-seronegative blood products, use of leukocyte-depleted blood products, high-dose ACV, GCV, foscarnet and standard or CMV hyperimmune immunoglobulin (Snydman, 1994; Martin, 1995; Paya, 1995). Other antiviral drugs, such as valaciclovir, cidofovir, benzimidavir and lobucavir are potential options for CMV management and are currently under investigation. In addition, in some transplant settings, 'pre-emptive' use of GCV has been studied. 'Pre-emptive therapy' is the term used for initiation of therapy at the time of the first CMV-positive assay but before symptomatic disease (Rubin, 1991). Cytomegalovirus management of patients at very high risk, such as during antilymphocyte therapy with OKT3, for rejection is called 'risk-adapted' prophylaxis. Many centres have combined strategies, but centres have arrived at different conclusions on the optimal combination of strategies in their setting.

Although definitions varied among reports, for this review, an attempt was made to use consistent definitions of CMV infection and CMV disease. The definitions as proposed at the *International Consensus Symposium on Advances in the Diagnosis, Treatment and Prophylaxis of Cytomegalovirus* (van der Meer et al., 1996) are as follows:

Cytomegalovirus infection is defined by isolation of the virus or by demonstrating its presence by immunologic or molecular techniques or by seroconversion. The techniques for identification of CMV viremia varied over time with earlier studies using conventional cell culture, then the shell vial assay and, more recently, pp65 antigenemia or PCR for CMV DNA.

Cytomegalovirus disease is diagnosed by considering the histologic evidence of disease, characteristic syndrome and exclusion of other etiologies in the presence of CMV infection.

2. Cytomegalovirus in BMT

In recent years, in BMT patients, 12–38% of allogeneic recipients and 4–11% of autologous recipients develop CMV disease (Meyers et al., 1986; Wingard et al., 1988; Reusser et al., 1990; Boeckh et al., 1996b; Hebart et al., 1997). Disease manifestations are fever, bone marrow suppression, interstitial pneumonia (IP), gastroenteritis, hepatitis and, rarely, retinitis. Cytomegalovirus infection is also associated with an increased risk of chronic graft-versus-host disease (GVHD) and opportunistic infections. IP is the leading cause of CMV-disease mortality in BMT. One-third of those with CMV reactivation or new infection develop IP, with a median onset at 40–50 days post-transplant. It is hypothesized that CMV-IP is an immunopathologic disease caused not only by the viral infection, but also by the host immune response (Grundy et al., 1987). This would be consistent with the increased risk of CMV-IP in allogeneic compared to autologous BMT recipients where there is increased immunosuppression associated with drug therapy for prevention and treatment of GVHD as well as acute GVHD itself.

Factors that have been associated with an increased risk of CMV infection and disease in BMT include (Meyers et al., 1986, 1990; Winston et al., 1990; Enright et al., 1993; Rubie et al., 1993; Gor et al., 1998):

- allogeneic BMT
- age of recipient (R)
- serostatus—CMV-positive recipient or donor (D)
- viral load
- total body irradiation
- transfusions from CMV-positive donors
- GVHD
- GVHD prophylaxis
- underlying disease

In most transplantation programs, the strategies used for prevention of CMV disease in autologous and allogeneic are different because of the significant difference in risk of disease and disease-associated mortality between these two groups of recipients. Therefore, autologous recipients are not included in the trials discussed in this paper and the conclusions cannot be generalized to autologous BMT recipients.

Since the serostatus of the recipient and donor are major factors for CMV disease, different

Table 1
Results of controlled trials using immune globulin for CMV in BMT[a]

Clinical outcome	Number of studies reporting outcome	Number of subjects		% with outcome	
		Ig group	C group	Ig group	C group
Symptomatic CMV infection	6	208	205	21	29
CMV pneumonia	10	514	565	9.5	14.5
Total mortality	8	403	406	45	51

[a] Ig, immune globulin; C, control.

strategies are necessary for different groups depending on their serostatus. Seronegative recipients acquire primary CMV infection predominantly from their donor marrow and transfusions with an approximate incidence of 40%. In several clinic trials, the use of screened CMV-seronegative blood products reduced the incidence of CMV infection to 4–9% (Bowden et al., 1986; Miller et al., 1991; Winston et al., 1993a). Similar results have been reported with the use of filtered blood products. In an RCT in 502 CMV-seronegative marrow recipients, CMV infection occurred in 1.3% of those who received only CMV-seronegative blood products and 2.4% of those receiving filtered blood products ($P = 1.0$) (Bowden et al., 1996). This indicates that for prevention of CMV infection in this setting, there is no significant difference between the use of seronegative blood products and filtered blood products.

A strategy that reduces exposure of seronegative BMT recipients to potentially infectious blood products is used in most transplant programs rather than immune globulin or antiviral prophylaxis for CMV disease.

2.1. Immune globulin in BMT

There are four recently published meta-analyses (Bass et al., 1993; Glowacki and Smaill, 1993; Messori et al., 1994; Wittes et al., 1996) and one critical review (Guglielmo et al., 1994) of the controlled trials on the effectiveness of immune globulin for prevention of CMV infection or disease in BMT. Many of the same trials are included in these analyses but the conclusions differ depending on the selection criteria for the trials. In 10 trials, hyperimmune globulin (CMVIG) was used (Winston et al., 1982; Meyers et al., 1983; Condie and O'Reilly, 1984; Winston et al., 1984; Kubanek et al., 1985; Vu Van et al., 1985; Bowden et al., 1986; Petersen et al., 1987; Ringden et al., 1987; Bowden et al., 1991) and in six trials, a conventional preparation of immune globulin (IVIG) was used (Condie and O'Reilly, 1984; Kubanek et al., 1985; Winston et al., 1987; Graham-Pole et al., 1988; Elfenbein et al., 1987; Sullivan et al., 1990). The dosing regimens varied among studies. The median of the mean duration of follow-up was 5 months. At the time of these studies, the strategy of using seronegative blood products for CMV-seronegative recipients was not routine. Antiviral agents were not used for CMV prophylaxis. Two meta-analysis included controlled trials of both CMVIG and IVIG (Bass et al., 1993; Glowacki and Smaill, 1993) and two meta-analysis included studies of CMVIG only (Messori et al., 1994; Wittes et al., 1996). All analyses were of controlled trials but in two, only randomized trials were included (Glowacki and Smaill, 1993; Messori et al., 1994) Table 1.

Despite the differences in inclusion criteria for the meta-analyses, there was some consistency in the results. All concluded that there was a significant beneficial effect of immune globulins in allogeneic BMT recipients in reducing the incidence of CMV infection with odds ratios (ORs) ranging from 0.44 to 0.60 with 95% confidence intervals (CIs) all under 1.00. The results of the effect of immune globulins on symptomatic CMV disease are more difficult to summarize because the trials included in the meta-analyses used difference outcome measures and the analyses of these measures differed amongst the meta-analyses. However, all

concluded that there was some effect on CMV symptomatic disease, such as CMV pneumonia, with ORs ranging from 0.44 to 0.6 but with wider CIs. In the meta-analyses, there was a significant effect on CMV-associated death with ORs ranging from 0.16 to 0.74.

All four meta-analyses concluded that immune globulin alone was efficacious in reduction of symptomatic CMV disease. However, prophylactic immune globulin has also been shown to be effective in reducing other major complications of BMT (Sullivan et al., 1990). In this study, the group at highest risk for GVHD, namely those >20 years of age showed a reduced incidence of GVHD (43 versus 28%, $P=0.029$) and a lower mortality rate (46 versus 30%, $P=0.023$). Also, although there was no effect on CMV infection, there was a reduction in CMV-IP (21 versus 9%, $P=0.003$). These results are supported by the results of the one meta-analysis that analyzed this fact—the OR for acute GVHD was 0.68 (95% CI of 0.45–1.02) and for non-CMV interstitial pneumonia, it was 0.57 (95% CI of 0.35–0.95). Since GVHD is an important risk factor for CMV disease, it is not clear whether the benefit of immune globulin is due to a direct effect on CMV infection or due to its effect on GVHD, a co-factor for CMV disease (Siadak et al., 1994).

In two of the meta-analyses (Bass et al., 1993; Glowacki and Smaill, 1993), the efficacy for CMVIG and IVIG were compared using the ORs for clinical outcomes compared with controls. There was no significant difference between types of immune globulin. There was a trend supporting a dose effect, in that the studies in which immune globulin was given about once a week for at least 3 months had the lowest ORs.

In several studies, the results could be stratified by CMV serostatus of the recipient. The efficacy of immune globulin for prevention of symptomatic CMV infection did differ by CMV serostatus of the recipient. Benefit was shown for CMV-seronegative recipients for whom the OR ($\pm$95% CI) was 0.55 (0.31–0.94) but not for CMV-seropositive recipients for whom the OR was 1.07 (0.41–2.80).

In CMV-seronegative recipients, there was clearly a reduction in symptomatic CMV disease with the use of immune globulin. However, almost all of these recipients received unscreened blood products. In a RCT comparing the prophylactic strategies of CMV-seronegative blood products alone or immune globulin therapy and CMV-seronegative blood products for CMV-seronegative BMT recipients ($n=51$), the incidence of CMV infection was 9 and 7%, of CMV pneumonia was 0 and 0%, and of acute GVHD was 48 and 20%, respectively (Winston et al., 1993a). These results suggest that CMV-seronegative blood products alone prevent most CMV infection and CMV disease in CMV-seronegative BMT recipients. However, these results support the role of immune globulin in prevention of acute GVHD.

When considering how to use the results of these studies and meta-analyses in practice today, it must be kept in mind that since those trials, techniques for CMV diagnosis have improved markedly and use of antiviral drugs such as GCV for prophylaxis and for pre-emptive therapy has increased.

3. Antiviral agents in BMT

3.1. ACV in BMT

In a trial in which ACV was used for prophylaxis of infection due to herpes simplex virus (Gluckman et al., 1983), it was found that the rate of CMV infection was lower in those taking ACV ($p<0.007$). This finding was supported by a study by Meyers et al. (1988) in which allogeneic BMT recipients who received IV ACV 500 mg/M^2/dose Q8H from day -5 to $+30$ were compared to controls over the first 100 days post-BMT. In the ACV group, there were lower rates of CMV infection ($P=0.0001$ by log-rank test), CMV disease ($P=0.008$) and of death ($P=0.0002$). In a RCT ($n=310$), allogeneic BMT recipients who were CMV-seropositive or those with a seropositive donor were randomized into three groups (A, B and C) (Prentice et al., 1994). Group A were given ACV intravenously (i.v.), 500 mg/M^2/dose Q8H from day -5 to $+30$, and ACV orally (p.o.), 800 mg QID from month $+1$ to $+6$. Group B

were given ACV i.v. day −5 to +30 and ACV p.o. month +1 to +6. Group C were given ACV p.o. day −5 to +30 and placebo p.o. month +1 to +6. They did not receive immune globulin. However, GCV was administered to some patients as pre-emptive therapy for CMV viremia (18, 21 and 22 patients in groups A, B and C). By day 210 after BMT, the incidence of CMV infection was 52, 49 and 61%, but the time to onset was 57, 54 and 41 days for groups A, B and C, respectively. After adjusting for CMV serostatus, the relative risk of developing CMV was no different for groups A and B, but both groups A and B had lower rates of CMV disease than group C. The relative risk (RR) with the 95% confidence interval was 0.69 (95% CI of 0.47–1.01) for group A versus C and 0.62 (95% CI of 0.42–0.91) for group B versus C. Similar but more modest effects were seen for the RR of CMV viremia and CMV disease. The probability of survival was highest for group A, using the Kaplan–Meier survival estimates for group A versus B and group A versus C, the respective log ranks were $P = 0.054$ and $P = 0.012$. This study suggests that the higher dose regimen was effective in reducing CMV infection. The effect may not be attributable to ACV alone since GCV was used pre-emptively in 20% of the patients (17% in group A, 20% in group B, 22% in group C). These patients have been enrolled in a long-term follow up study (Prentice et al., 1997). The group receiving ACV i.v. then p.o. had a significantly reduced risk of CMV disease and a 19% survival advantage 1 year after BMT compared with the other two groups.

3.2. GCV in BMT

GCV is an ACV derivative which has increased in vitro activity against CMV (Plotkin et al., 1985). Initial trials in which GCV was used for treatment of CMV pneumonia in BMT recipients showed no improvement in the outcome of CMV infection. (Shepp et al., 1985; Erice et al., 1987; Winston et al., 1988). There was concern about the relative benefit of reduction in CMV disease compared to the harm caused by toxicity particularly neutropenia and by viral resistance if GCV were used prophylactically. Concerns about the myelosuppressive effect and development of resistance have shown to be real issues. CMV resistance to GCV does occur in transplant recipients who have received GCV (Drew et al., 1991; Reusser et al., 1996; Erice et al., 1997; Rosen et al., 1997). In order to reduce the number of patients receiving GCV and to shorten the duration of exposure to GCV, trials have been conducted to evaluate the effect of GCV as early treatment, which has been called pre-emptive therapy.

3.3. Pre-emptive GCV for BMT

In the pre-emptive approach, patients are who are at high risk of CMV disease are identified by recovery of CMV from surveillance of blood, bronchoalveolar lavage (BAL) fluid, urine or pharyngeal washings. These patients are then treated with GCV and continued on prophylactic GCV therapy to day 100 or 120 post-transplant. In the first two trials of pre-emptive therapy, in one, GCV was used in combination with IVIG (Schmidt et al., 1991) and in the other, GCV was used alone (Goodrich et al., 1991).

In the study by Schmidt et al. (1991), 104 allogeneic BMT recipients underwent BAL at day 35. The 40 patients who were CMV-positive by shell-vial cultures of the BAL fluid were randomized to GCV or observation groups. The GCV was given as 5 mg/kg BID for 14 days followed by 5 mg/kg/day until day 120. All patients received IVIG (500 mg/kg) every other week from day −9 to 180. Fifteen of 64 (23%) patients who were not identified by CMV culture developed CMV disease. This indicated that this screening method needed to be improved to identify a larger proportion of high-risk patients. In the group receiving GCV and IVIG compared to the group receiving IVIG alone, the incidence of CMV pneumonia or death was 25 versus 70% ($P = 0.01$).

In the study by Goodrich et al. (1991), 281 allogeneic BMT recipients, who were CMV-seropositive or who received seropositive marrow, were screened for CMV excretion by weekly cultures of throat swabs, blood or urine following transplantation. Seventy-two (26%) were culture

positive and were randomized to receive either placebo or GCV (5 mg/kg BID) for 7 days followed by 5 mg/kg/day until day 100. All patients received high doses of ACV for a maximum of 30 days after transplant. Of the culture negative group, 35 of 209 (17%) developed CMV disease. This indicated that this method of screening needed to be improved to identify a larger proportion of the high-risk patients. Of those identified as CMV culture positive, by day 100, only one of 37 (3%) treated versus 15 of 35 (43%) in the placebo group had developed CMV disease ($P = 0.00001$). Overall survival of the GCV-treated group was better than that in the placebo group at day 100 and 180 ($P = 0.041$ and 0.027, respectively).

Although the screening method for these two studies differed, both studies demonstrated the efficacy of GCV as pre-emptive therapy in reducing CMV disease and improving survival. But in both studies the screening method needed to be improved to identify a larger proportion of high-risk patients. The study by Schmidt et al. (1991) also indicates that GCV + IVIG is superior to IVIG alone for pre-emptive therapy for CMV disease. In a prospective trial by Bacigalupo et al. (1992), 98 consecutive allogeneic BMT recipients were monitored with weekly CMV cultures and there was a reduction in CMV disease (20 versus 50%) and mortality rate (18 versus 42%) in the GCV + IVIG compared with placebo + IVIG group. None of these studies provide information for comparing GCV + IVIG with GCV alone for pre-emptive therapy for CMV disease.

CMV infection can be detected earlier by PCR than by conventional and shell vial culture assays (Einsele et al., 1991; Wolf and Spector, 1993; Einsele et al., 1995). In a prospective study, 71 patients received pre-emptive GCV therapy based either on the PCR technique (37) or on culture assays (34). GCV was given until clinical signs resolved and PCR negativity was documented. The median day of detection of CMV was 32 versus 49 ($P = 0.006$). The incidence of CMV disease was 2/37 versus 8/34 ($P = 0.02$) and that of CMV-associated mortality, 0/37 versus 5/34 ($P = 0.02$). Therefore, pre-emptive therapy based on a more sensitive detection method reduces the incidence of CMV disease and CMV-related mortality.

3.4. Prophylactic GCV for BMT recipients

In a small prospective trial ($n = 25$), GCV was given at a dose of 5 mg/kg twice daily from day -8 to -1 and restarted at day 21 or when the neutrophil count reached 0.750×10^{-9}/l (Atkinson et al., 1991). When the GCV group was compared to a matched control group ($n = 40$), the incidence of CMV infection was 0 versus 23% ($P = 0.02$) and CMV pneumonia was 0 versus 17% ($P = 0.05$). Subsequently, two RCTs have been conducted, in which GCV was used for CMV prophylaxis in allogeneic BMT recipients (Goodrich et al., 1993; Winston et al., 1993b) (see Table 2).

Goodrich et al., 1993 studied 63 CMV-seropositive allogeneic BMT recipients, who were randomized to receive either GCV i.v. from engraftment as 5 mg/kg twice daily $\times$ 5 days then once daily to day 100 or placebo. Engraftment was defined as an absolute neutrophil count of 0.750×10^{-9}/l. High-dose ACV was given from the time of conditioning to engraftment. It is not clear whether or not patients received any immune globulin. Patients who began to excrete CMV were treated pre-emptively with GCV. CMV was detected by shell-vial and conventional culture methods. The duration of follow-up was 180 days with outcome assessments at 100 and 180 days. Winston et al., 1993a,b studied 85 CMV-seropositive BMT recipients, who were randomized to receive either GCV 2.5 mg/kg Q8H from day -8 to -1 Q8H and then GCV 6 mg/kg once daily Monday–Friday from engraftment to day 120 or placebo. Engraftment was defined as an absolute neutrophil count of 1.0×10^{-9}/l. There was no other CMV prophylaxis. The patients were followed to day 120 post-transplant Table 2.

These two trials demonstrated that GCV alone was effective in reducing CMV infection ($P = 0.001$ and 0.0009 for Goodrich et al. (1993) and Winston et al. (1993b), respectively) and in reducing CMV disease ($P = 0.001$ and 0.09, respectively). However, there was no survival benefit

Table 2
The results of two RCTs of ganciclovir prophylaxis for CMV in BMT

	Goodrich		Winston	
	Placebo group ($n = 31$)	Ganciclovir group ($n = 33$)	Placebo group ($n = 45$)	Ganciclovir group ($n = 40$)
Patients with CMV infection, *n* (%)	14 (45)	1 (3)	25 (56)	8 (20)
Patients with CMV disease, *n* (%)	9 (29)	0	11 (24)	4 (10)
Patients with neutropenia, *n* (%)	0[b]	10 (30)[b]	13 (28)	25 (58)
Survival	25 (81)	29 (88)	29 (64)	28 (70)
	23 (74)*	23 (70)[a]		

[a] At day 180 after transplant.
[b] During the blinded phase of the study only.

and there was significant morbidity due to the neutropenia caused by GCV. Also, in the trial by Goodrich et al. (1993), the control group who received pre-emptive GCV using culture methods for detection of CMV still had 29% incidence of CMV disease.

One approach to try to reduce the toxicity related to GCV, is to use a lower dose of GCV for prophylaxis. In a prospective uncontrolled study by Przepiorka et al. (1994), GCV was given to recipients of T-cell depleted marrow as 2.5 mg/kg three times daily on days -8 to -2 and 5 or 6 mg/kg three times per week from engraftment to day 100. They also received weekly IVIG and screened or filtered blood products. GCV at this dose was found to be moderately myelosuppressive and not effective in preventing CMV infection.

In RCT (Boeckh et al., 1996a), prophylactic GCV therapy was compared with pre-emptive therapy. CMV was detected in blood samples by CMV antigen testing for pp65 antigen. Of the 226 eligible patients, 112 received prophylactic GCV from engraftment and 114 were monitored for pre-emptive therapy. All patient received either routine IVIG or IVIG if hypogammaglobulinemic. More patients in the pre-emptive group than in the prophylactic group developed CMV disease (14 versus 2.7%, $P = 0.002$), but there was no significant difference in CMV disease by day 180. CMV-related death and neutropenia was not significantly different between groups. In the GCV prophylactic group, there was a higher incidence of invasive fungal infection ($P = 0.03$) and more GCV was used ($P < 0.0001$). This study indicates that GCV prophylaxis is more effective in prevention of CMV disease than is pre-emptive GCV therapy. But GCV prophylaxis is associated with more early invasive fungal disease and more late CMV disease resulting in similar survival rates. In other words, there is a trade off of CMV-related morbidity for drug-induced toxicity.

3.5. Risk-adapted approach to GCV prophylaxis in BMT

In the risk-adapted approach, CMV-seropositive patients were assigned to receive GCV when either (1) CMV antigenemia was detected (pre-emptive therapy) or (2) when high-dose steroids were given for grade II GVHD (prophylactic therapy). In a prospective, uncontrolled study of this approach, 41 CMV-seropositive were followed for 180 days (Verdonck et al., 1997). The GCV dose for pre-emptive or prophylactic therapy was 2.5 mg/kg i.v. twice daily. GCV was given to 29% of patients prophylactically and 17% pre-emptively. None developed CMV pneumonia. GCV-related neutropenia was mild. This appears to be a promising approach for CMV prevention in BMT recipients.

3.6. Foscarnet for prophylaxis in BMT recipients

To date, most of the trials using foscarnet for prevention of CMV disease in BMT recipients are small uncontrolled trials. As with GCV, foscarnet was not very effective when used for treatment of CMV pneumonia (Aschan et al., 1992).

Bacigalupo et al. (1994) reported an open trial using either GCV or foscarnet for pre-emptive therapy. CMV infection was diagnosed by CMV antigenemia. In 25 patients, both agents were effective in clearing antigenemia and survival at 1 year in the foscarnet versus GCV group was 62 versus 69%. A phase II study was conducted using foscarnet as pre-emptive therapy based on leukocyte-based PCR detection of CMV disease (Ljungman et al., 1996). In 14 allogeneic BMT recipients, none developed CMV disease and the dose of 60 mg/kg twice daily was well tolerated. When foscarnet combined with GCV was used in pre-emptive therapy using CMV antigenemia for CMV detection, the actuarial 1-year transplant-related mortality rate was 13% compared with 47% for matched controls receiving single-drug therapy (Bacigalupo et al., 1996).

Foscarnet was studied in a phase I–II trial for prophylaxis of CMV infection (Reusser et al., 1992). In 19 CMV-seropositive BMT recipients, who received foscarnet from day -1 to $+30$ as 40 mg/kg every 8 h and then 60 mg/kg daily until day $+75$, only four developed CMV infection and none developed CMV disease. Rapid impairment of renal function occurred in three patients receiving concomitant amphotericin B. Foscarnet has also been studied for prevention of CMV infection in BMT recipients unable to receive GCV (Ippoliti et al., 1997). Foscarnet was given when prophylactic GCV was unable to be given because of delayed engraftment or GCV-induced neutropenia. Foscarnet was well tolerated and 5% developed CMV disease.

From these preliminary studies with foscarnet, the pre-emptive approach with either a single drug or combination drugs looks promising (Ljungman et al., 1996). Controlled trials are needed to evaluate the efficacy of these approaches.

3.7. Immune globulin and GCV for BMT

There are no reported RCTs in which the efficacy of the combination of GCV and immune globulin is compared to GCV alone for CMV prophylaxis, but there are two prospective trials with combinations compared with historical controls who received immune globulin but no GCV (Yau et al., 1991; von Bueltzingsloewen et al., 1993). In both trials, GCV and ACV were given in a similar schedule to that in the trial by Winston et al. (1993a,b) Hyperimmune globulin was given weekly from day -7 to $+90$ to 82.5% of patients in the study by von Bueltzingsloewen et al. (1993) ($n=33$). Immune globulin was given every 2 weeks from day -2 to day $+250$ in the study by Yau et al. (1991) ($n=14$). In both trials, the combination of immune globulin and GCV was more effective than immune globulin alone as a prophylactic strategy leading to a significant decrease in CMV infection and CMV pneumonia. However, in the study by von Bueltzingsloewen using CMVIG there was no survival benefit. The overall survival to day 120 was 52.8% in the GCV + CMVIG group and 62.1% in the CMVIG alone group. In the study by Yau et al. (1991), overall survival was 85.9% in the GCV and IVIG group and 56.7% in the IVIG alone group. Without controlled studies comparing the combination of GCV and IVIG with GCV alone, it remains inconclusive whether immune globulin in combination with GCV is more effective than GCV alone for CMV prophylaxis for allogeneic BMT recipients.

3.8. Summary for BMT recipients

The most effective strategy for prevention of CMV disease in allogeneic BMT recipients who are seropositive or who receive seropositive marrow is GCV prophylaxis. With a long course of GCV for prophylaxis, CMV disease was reduced to 0–10%. However, there is a trade-off of CMV morbidity with toxicity of GCV which leads to little survival benefit. The significant toxicity of GCV when used early post-BMT means that this strategy is not optimal for management of CMV disease in BMT. Pre-emptive GCV therapy using

either antigenemia or PCR methods for diagnosis of CMV infection has been shown to be effective in reducing CMV disease and increasing survival. Strategies using the risk-adapted approach also appear useful but need further study. Of the other antiviral agents, ACV is less effective than GCV for prevention of CMV infection in BMT recipients. Further study is needed to compare the efficacy of foscarnet and GCV in this setting.

There are no controlled trials comparing the combination of IVIG and GCV prophylaxis with GCV alone. Since the benefits of IVIG for reduction of other complications of BMT have led to immune globulin use in many BMT centres, it is unlikely that controlled trials to confirm the benefit of combination GCV and IVIG compared to GCV alone will be conducted.

4. CMV in solid organ transplantation

4.1. Renal transplantation

There have been advances in the care of organ transplant recipients, so that since 1990, the morbidity and mortality caused by CMV infection post-transplant has been much reduced. The major consequences of CMV infection are CMV disease, superinfection with opportunistic pathogens and injury to the transplanted organ (Richardson et al., 1981; Rubin, 1994). In renal transplant recipients, CMV disease may cause constitutional symptoms such as fever, which is called the CMV syndrome, or may cause organ-specific disease, the most common sites are the gastrointestinal tract and the lungs. Factors that predispose renal transplant recipients to CMV infection include CMV-seropositive donor or recipient, CMV-positive blood products, cadaveric donor, donor-recipient HLA mismatch and acute rejection immunotherapy (Glenn et al., 1981). More recently, viral load has also been shown to be a major risk factor for CMV disease (Cope et al., 1997b). The patients at highest risk for CMV disease after transplantation are those who are seronegative and receive a CMV-seropositive organ from a cadaveric donor. The strategies that have been used to reduce CMV disease in renal transplant are prophylaxis with immune globulin or ACV and pre-emptive therapy with GCV Table 3.

4.1.1. Immune globulin for renal transplant recipients

There are two RCTs and four prospective, non-randomized controlled trials evaluating IVIG for renal transplant recipients (Kasiske et al., 1989; Steinmuller et al., 1989; Khawand et al., 1989; Steinmuller et al., 1990; Conti et al., 1993) (Table 3). There are three randomized and one prospective non-randomized trial of CMVIG for renal transplant recipients (Fassbinder et al., 1985, 1986; Snydman et al., 1987, 1991) Table 4.

In a review by Dickinson et al. (1996), the efficacy of IVIG and CMVIG for prevention of CMV disease in renal transplant recipients was compared using weighted average incidence of CMV syndrome and disease in the treated and control groups of the studies in the tables ($n = 590$). The results are shown in Table 5.

Although there are differences in doses, schedules, patient populations and study design, most of the studies, individually and then combined, show a reduction of CMV syndrome and disease with prophylactic immune globulin therapy. The efficacy of IVIG and CMVIG appear similar. This is further supported by the RCT by Fassbinder et al. (1986) in which IVIG and CMVIG were compared and there was no significant difference in CMV infection between the groups (67 versus 56%). Unfortunately, the results for CMV syndrome and disease were not reported in that study.

4.1.2. ACV for renal transplant recipients

There is one RCT ($n = 104$) evaluating ACV in renal transplantation (Balfour et al., 1989). Patients were of mixed donor and recipient status and donors were cadaveric. ACV was given p.o. as 800 mg Q6H from day -1 to $+98$ with dose adjustment for renal function. CMV infection occurred in 61% of controls and 31% of the ACV group ($P = 0.01$). CMV disease occurred in 17% of the controls and 2% of the ACV group ($P = 0.017$). This study provided strong evidence for the efficacy of ACV for reduction of CMV disease

Table 3
Results of trials using IVIG for CMV in renal transplantation

Reference	Design	Patient population	Regimen	CMV syndrome		CMV disease	
				IVIG (%)	Control (%)	IVIG (%)	Control (%)
Steinmuller et al., 1990	RCT	$n=34$	IVIG	12	39	0	33
		R+ CD, LRD	Q2wk×5	$P=0.13$		$P=0.02$	
Kasiske et al., 1989	RCT	$n=28$	IVIG×1 pre	77		0	0
		Any CMV serostatus CD	Q1wk×12	$P>0.05$			
Conti et al., 1993	CT, non-R	$n=56$	IVIG×1 pre	33	39	2	26
		D+/R− CD, LRD	Q1wk×5	$P=$ NS		$P<0.05$	
Conti et al., 1994	CT, historic control	$n=51$	IVIG×1 pre	22	39	4	26
		D+/R− CD, LRD	Q1wk×7	$P=$ NS		$P<0.05$	
Steinmuller et al., 1989	CT, non-R	$n=47$	IVIG×1 pre	26	63	NR	
		D+/R− CD, LRD	Q2wk×4	$P<0.02$			
Khawand et al., 1989	CT, non-R	$n=18$	IVIG×1 pre	70	50	0	25
		D+/R− CD, LRD	Q2wk×2				

R−, recipient CMV-seronegative; D+, donor CMV-seropositive; CD, cadaveric donor; LRD, living related donor; RCT, randomized controlled trial; CT, non-R, controlled trial, non-randomized.

in renal transplant recipients. Two uncontrolled trials by Fletcher et al. (1988) and Vasquez et al. (1993) supported these results.

4.1.3. ACV versus ACV + immune globulin for renal transplant recipients

There are two trials comparing ACV alone with the combination of ACV and immune globulin in renal transplant recipients who were R–D+ (Bailey et al., 1993; Carrieri et al., 1995). In both trials, ACV was given as 800–3200 mg per day p.o. according to the patients renal function for 3 months. Bailey et al. (1993) conducted a small RCT ($n=21$) in solid organ transplant recipients, 14 of whom were renal transplant patients. CMV disease occurred in 5/8 (62%) of the ACV alone group and 5/6 (83%) of the combination group. CMV pneumonia occurred in none of the ACV alone group but 1/6 (17%) of the combination group. This study showed no significant differences in the outcomes of the groups but the sample size is very small. The study by Carrieri et al. (1995) is larger ($n=116$) but retrospective. At a single transplant center, for 17 months the protocol for CMV prophylaxis for R–D+ recipients was high-dose ACV alone ($n=43$) and was subsequently changed to ACV + CMVIG ($n=73$). The study groups had similar baseline characteristics and received similar immunosuppressive therapy. The rates of CMV disease in the ACV versus ACV + CMVIG groups were 47 versus 23% ($p=0.01$). CMV pneumonia occurred in five patients on ACV alone and none in the combination group. No deaths were attributable to CMV. Although this was a retrospective study which could only provide weak evidence, it suggested that the combination of ACV and CMVIG was more effective than ACV alone for reduction in

Table 4
Results of trials using CMVIG for CMV in renal transplantation

Reference	Design	Patient population	Regimen	CMV syndrome		CMV disease	
				CMVIG (%)	Control (%)	CMVIG (%)	Control (%)
Snydman et al., 1987	RCT	$n=59$ D+/R− CD,LRD	CMVIG day −1, weeks 2, 4, 6, 8, 12, 16 Placebo day −1, weeks 2, 4, 6, 8, 12, 16	21 $P<0.01$	60	13 $P<0.01$	46
Fassbinder et al., 1985	RCT	$n=11$ D+/R− CD	CMVIG day −1, +18, 38, 58, 78 Control: IVIG day −1, +18, 38, 58, 78	0	71	NR	NR
Fassbinder et al., 1986	RCT	$n=76$ D+ CD, LRD	CMVIG day −1, +18, 38, 58, 78 Control: IVIG day −1, +18, 38, 58, 78	NR	NR	NR	NR
Snydman et al., 1991	CT, non-R	$n=36$ D+/R− CD, LRD	CMVIG wk 0, 2, 4, 6, 8, 12, 16	36 $P=0.04$	60	22 $P=0.053$	46

CMV disease, reducing both incidence and severity of disease.

4.1.4. GCV for renal transplant recipients

A RCT was performed to compare prophylaxis using a 21-day course of 2.5 mg/kg i.v. GCV daily (or less according to renal function) ($n=24$) with 6 weeks of weekly IVIG ($n=27$) for prevention of CMV disease in R−D+ renal transplant patients (Conti et al., 1994). The GCV group also received preemptive GCV if there was a rejection episode requiring treatment with OKT3. The results were also compared to a historical control group ($n=23$) who did not receive any CMV prophylaxis. The rates of CMV syndrome in the GCV, IVIG and control groups were 21, 22 and 39%, respectively. The rates of CMV disease were 0, 4 and 26%, respectively. No deaths in the RCT were due to CMV disease but three deaths in the historical group were due to CMV disease. This study indicates that GCV if used as prophylaxis with preemptive GCV during treatment of rejection, there is similar efficacy for CMV prophylaxis as using IVIG prophylaxis. The comparison with historical controls supports previous studies showing a benefit of prophylaxis versus no prophylaxis.

In an RCT study by Pouteil-Noble et al. (1996) ($n=50$), the efficacy of 2 weeks of GCV + ACV to complete 3 months was compared to placebo for CMV prophylaxis in all recipients. The recipients were stratified by R and D status. In the treatment and control groups, there were four versus five patients who were R−D+. There was a significant reduction in the occurrence of

Table 5
CMV syndrome and disease in renal transplant recipients receiving IVIG or CMVIG

Prophylactic	CMV syndrome		CMV disease	
agent	Treated (%)	Control (%)	Treated (%)	Control (%)
IVIG	32	49	2	19
CMVIG	30	61	20	53

viremia (log-rank test, $P = 0.005$) and CMV disease occurred in 6/24 (25%) of the GCV + ACV group and 14/26 (54%) of the placebo group. No deaths were reported. Although this study supports the efficacy of GCV + ACV, it is difficult to compare with other trials because the results for the high-risk group (R−D+) were not specified.

4.1.5. GCV + immune globulin for renal transplant recipients

In a RCT, a short course of GCV plus immune globulin prophylaxis was compared with a 3-month course of ACV for prophylaxis in solid organ transplants ($n = 266$), 143 of whom were renal transplant recipients (Dunn et al., 1994). GCV (5 mg/kg i.v. Q12H) plus CMVIG or IVIG was given for 7 days. ACV prophylaxis consisted of 800 mg p.o. or 400 mg i.v. QID. Doses of ACV and GCV were adjusted for renal dysfunction. In the renal transplant group, ACV was more effective than GCV + CMVIG for reduction in CMV disease (16 versus 24%). In all transplant groups, the biggest difference was seen in the R−D+ group, where the rates of CMV disease were 25 versus 55%. However the survival of the two groups were similar. This trial demonstrates that for renal transplant recipients, a short course of GCV, even if combined with IVIG, is less effective for CMV prevention than a long course of ACV.

4.1.6. Risk-adapted and pre-emptive GCV for renal transplant recipients

The efficacy of risk-adapted GCV for seropositive renal transplant recipients when they receive antilymphocyte antibody preparations has been studied in two trials (Conti et al., 1995; Hibberd et al., 1995). In both studies, GCV was effective in reducing the incidence of CMV disease (9 versus 56%, $P < 0.05$ in one study and 14 versus 33%, $p = 0.018$ in the other). There are no reported studies of pre-emptive therapy for R−D+ renal transplant recipients (Abecassis et al., 1997a,b).

4.1.7. Summary for renal transplant recipients

In renal transplantation, the highest risk group is the R−D+ recipient. For the R−D+ group, prophylaxis with ACV alone for 3 months, GCV for 3 weeks with pre-emptive GCV during rejection episodes, or immune globulin for at least 8 weeks have all been effective in preventing CMV disease. There is one retrospective study which can only provide weak evidence that indicated that the combination of ACV and CMVIG was more effective than ACV alone for reduction in CMV disease in R−D+ recipients, reducing both the incidence and severity of disease. However, the outcomes in the combination group in that study were similar to that in the single strategy groups listed. Therefore, to date, there are no prospective trials which provide evidence to compare the efficacy of combination therapy with either antiviral or immune globulin therapy alone for renal transplant recipients.

For the sero-positive recipients, risk-adapted GCV during treatment for rejection has been shown to be an effective strategy without being combined with other prophylactic strategies.

4.2. Liver transplantation

Prior to 1990, CMV was the most common cause of infection following liver transplantation, with an incidence of 20–60% and ~50% of infected patients developing CMV disease (Stratta et al., 1989). As in other organ transplantation

recipients, CMV infection causes not only CMV disease but also increases the risk of opportunistic infections (Collins et al., 1994) and allograft rejection (O'Grady et al., 1988; Paya et al., 1989). CMV infection, particularly primary infection, has been associated with an increased risk of not only invasive fungal infection, but also bacteremia (Paya et al., 1993; Collins et al., 1994; Hadley et al., 1995; Falagas et al., 1996). The major risk factors for CMV disease are the seropositive donor and immunosuppressive agents, particularly antilymphocyte therapy. Recently, viral load and quantity of methylprednisolone have also been associated with increased risk of CMV disease (Cope et al., 1997a). Most of the controlled trials of CMV prophylaxis in liver transplantation include all R and D serostatus and the R−D+ group are usually a small proportion of the total. Since the R−D+ group is at higher risk for CMV disease, the optimal strategy for prevention in this group may differ from that for seropositive recipients and R−D− recipients.

4.2.1. Immune globulin for liver transplant recipients

In a multicenter RCT, the efficacy of CMVIG was compared to placebo in liver transplant patients ($n = 141$) (Snydman et al., 1993). CMVIG was given pre-transplant and continued to week 16. Over a 1-year follow-up, rates were reduced for CMV disease from 31 to 19% ($P = 0.11$), for death associated with CMV from 18 to 9% ($P = 0.10$), and for invasive fungal disease from 18 to 7% ($P = 0.04$). In the stratified analysis, there was no benefit for the R−D+ recipient with CMV infection occurring in 53% in both groups ($n = 19$ per group) and CMV-associated disease (including fungal infection) occurring in 47 and 37%, respectively.

Snydman et al. (1994) subsequently reported on the R−D+ group who received CMVIG in an open-label study. When they combined the results of the RCT and the open-label study, they report that, comparing CMVIG to placebo for R−D+ recipients, CMV disease occurred in 13/28 (46%) versus 10/19 (53%) and severe disease in 7/28 (25%) versus 9/19 (47%). However, there are major confounding factors in the open-label study because there was a reduction in the use of OKT3 and approximately one-third received high-dose ACV for 3 months.

4.2.2. ACV for liver transplant recipients

In the clinical trials in which ACV was used for prophylaxis of CMV disease, ACV was given for 3–4 months. In the controlled trial by Saliba et al. (1993) for seropositive recipients, ACV alone reduced the rate of CMV disease from 31 to 19% ($P = 0.01$). In trials in which recipients and donors of all serostatus were included, the incidence of CMV disease using ACV alone for 3–4 months ranged from 10 to 29%. This is consistent with a relative lack of effectiveness of ACV alone for the R−D+ group. The results of the trial comparing ACV and GCV are discussed Section 4.2.3.

4.2.3. GCV for liver transplant recipients

Very low rates of CMV disease have been reported in the trials using GCV as prophylaxis. The lowest rates of 0 and 0.8% were reported in the trials where GCV was used for 16 weeks and 100 days, respectively (Prian and Koep, 1994; Winston et al., 1995b). In a RCT in liver transplant recipients, the effect of GCV as 6 mg/kg/day i.v. from day 1 to 30, then 6 mg/kg/day Monday–Friday until day 100 was compared to ACV 10 mg/kg i.v. Q8H from day 1 to discharge, then 800 mg p.o. QID until day 100. During the first 120 days after transplant, the incidence of CMV infection was significantly reduced by GCV compared to ACV (5 versus 38%, $P < 0.0001$), as was CMV disease (0.8 versus 10%, $P = 0.002$). GCV was well tolerated with similar incidence of leukopenia and renal failure in the two groups. This study confirms that in this setting, GCV for 100 days is more effective than ACV for 100 days.

The duration of antiviral prophylaxis also appears to be an important factor in prevention. When GCV was used for only 7 days, the rate of CMV disease was 67%, higher than any other prophylactic regimen (Dunn et al., 1994). When GCV was given in the third and fourth weeks after transplantation, there was a similar incidence of CMV disease in the prophylaxis and control groups (27 versus 34%) (Cohen et al.,

1993). In two RCTs, an initial 2 weeks of GCV followed by ACV for 10 weeks was more effective than ACV alone for 12 weeks (Martin et al., 1994; Badley et al., 1997). The incidence of CMV disease was reduced from 28 to 9% ($P < 0.001$) and from 23 to 11% ($P = 0.03$). In one controlled trial (Green et al., 1994), there did appear to be a benefit when 2 weeks of GCV and 10 weeks of ACV were compared to 2 weeks of GCV alone, with CMV disease occurring in 20 and 5%, respectively. However, this was a small study ($n = 29$) so the results must be interpreted with caution.

In the initial studies, GCV was given i.v. because of the poor bioavailability of oral GCV. However, recent studies giving GCV orally have shown this route to be effective. In a RCT, 304 liver-transplant recipients were randomized to receive either oral GCV 1000 mg or placebo three times per day, starting as soon as the patient could take medication by mouth until day 98 post-transplant (Gane et al., 1997); R−D− patients were excluded. At 6 months, the incidence of CMV disease was 18.9% in the placebo group and 4.8% in the GCV group ($P < 0.001$). In the R−D+ group, the incidence of CMV disease was 44 and 14.8%, respectively. There were no major adverse events and GCV was not associated with significant myelotoxicity in this study. This study demonstrates that oral GCV is a safe and effective method of prevention of CMV disease after liver transplantation. The major limitation of this method is that sicker patients who cannot take medications by mouth are excluded. However, those patients could receive i.v. GCV instead.

In many of these studies, the group at risk of primary disease were analyzed separately. In the study by Martin et al. (1994), primary CMV infection was not significantly reduced with the addition of GCV, occurring in 7/14 (50%) of the GCV + ACV group and 11/17 (65%) of ACV-alone group ($P = 0.2$). However, CMV disease was reported as less severe in the GCV + ACV group, although numbers are not reported. In the study by Badley et al. (1997), similarly, there was not a significant effect on CMV infection in the R−D+ group (83 versus 75%, $P = 0.27$) but CMV disease was reduced from 58 to 25% ($P = 0.04$). Even when GCV was continued for 100 days, although there was a trend for reduction in the rate of primary CMV infection compared with ACV prophylaxis (11 versus 42%, $P = 0.06$), there was no significant effect on CMV disease (6 versus 16%, $P = 0.60$). In the study by Gane et al. (1997), oral GCV for 6 months was effective in preventing CMV disease in all subgroups including the high-risk group, R−D+. However, using oral GCV, the incidence of CMV disease in this high-risk group was still 14.8%. Additional strategies are needed to further reduce CMV disease for this group.

4.2.4. GCV + immune globulin for liver transplant recipients

There are five studies in which GCV and immune globulin are combined for CMV prophylaxis. Three are prospective controlled trials and two are retrospective. In the RCT by Dunn et al. (1994), the combination prophylaxis was less effective than ACV alone, probably because 7 days of prophylaxis is too short. In the RCT by King et al. (1997) ($n = 56$), when GCV was given for 1 month with IVIG for 16 weeks, the rate of CMV disease in a R−D+ group was 17% compared with 26% in the group receiving IVIG alone. This difference was not statistically significant ($P = 0.42$). In another RCT, the effect of GCV and IVIG was compared to ACV and IVIG in 104 liver transplant recipients (Nakazato et al., 1993). Both GCV and ACV were given as 5 mg/kg/day i.v. until discharge then oral ACV as 5 mg/kg/day for 3 months. IVIG was given twice weekly until discharge from hospital. The GCV combination was significantly more effective than the ACV combination in reducing the incidence of CMV disease for 3 months post-transplant (3.8 versus 15%, $P < 0.05$). In the retrospective studies in which GCV and immune globulin were combined for prophylaxis, the rate of CMV disease in the R−D+ groups was 0% when GCV + CMVIG were given for 16 weeks (Prian and Koep, 1994) and 7% when GCV was given for 2 weeks and CMVIG for 16 weeks (Ham et al., 1995). The only study in which similar low rates for CMV disease have been reported in the R−D+ group is in the study by Winston et al. (1995b) in which the rate for R−D+ on GCV for 100 days was

10%. One possibility is that the longer course of 100 days or 16 weeks of GCV is the major factor in prevention, rather than the combination with IVIG.

It therefore remains inconclusive for the R– D+ liver transplant recipient whether the combination of GCV (or GCV followed by ACV) with immune globulin would be more effective than a long course of GCV (100 days or 180 days) alone Table 6.

4.2.5. Pre-emptive and risk-adapted therapy for liver transplant recipients

Two approaches have been taken to using pre-emptive or risk-adapted GCV therapy in liver transplantation. The 'risk-adapted' approach is one in which GCV is started when treatment with antilymphocyte therapy such as OKT3 is started for rejection. The pre-emptive approach is similar to that for BMT recipients, in which GCV is started when surveillance specimens for CMV are positive. Initially, CMV cultures were used for surveillance and more recently PCR and other molecular techniques such as pp65 antigenemia for detection of CMV viremia.

In an RCT of 100 liver transplant patients receiving OKT3, the effect of oral ACV 400 mg five times a day (dose reduced for those <40 kg) for 3 months and IVIG six doses over 4 weeks was compared to a control group who did not receive either prophylaxis. (Stratta et al., 1992) The prophylactic regimen did not significantly reduce the incidence of CMV infections but did significantly reduce the incidence of other viral infections, major fungal infections and deaths due to sepsis. This led to a significant improvement in survival in the prophylactic group.

In an open trial of 51 consecutive liver transplant recipients receiving OKT3 for rejection, GCV was given for at least 4 weeks (Winston et al., 1995a). In patients who received more than 4 weeks of GCV, only one (2.2%) developed CMV disease (hepatitis). In another open prospective study of 69 liver transplant patients receiving OKT3, GCV 10 mg/kg/day was given for 14 days (Lumbreras et al., 1993). Compared with historical controls, there was a significant reduction in CMV disease (52 versus 12%, $P<0.01$).

In an RCT ($n=47$), comparing pre-emptive GCV with high-dose ACV as prophylaxis CMV shedding was measured by using shell vial cultures of buffy coat and urine (Singh et al., 1994). CMV disease occurred in 4% of the GCV group compared with 29% of the ACV group ($P<0.05$).

Both the 'risk-adapted' and 'pre-emptive' approaches are therefore promising approaches for selected groups of transplant patients. For the pre-emptive strategy, the benefit of the strategy is dependent on the sensitivity of the laboratory tests because earlier detection of CMV viremia leads to a larger proportion of patients at risk of CMV disease being identified early. Although pre-emptive therapy reduces the drug costs by shortening the duration of therapy, some of the costs may be offset by increased laboratory costs of surveillance.

4.2.6. Summary for liver transplant recipients

Each of the prophylactic strategies—immune globulin, ACV, and GCV—were shown to reduce the incidence of CMV disease (see Table 6). The effect tended to be greater for GCV than for either ACV or immune globulin. The effect tended to be greater if the antiviral prophylaxis was continued for 14–16 weeks post-transplant, reaching almost total prevention for the groups other than the R–D+ group when GCV was used for 14–16 weeks. The best results to date for the R–D+ group have been with a long prophylactic course of oral GCV. Based on the results from clinical trials, it remains inconclusive whether for this high-risk group, the combination of GCV (or GCV followed by ACV) with immune globulin would be more effective than a long course of GCV (100 days or 180 days) alone.

4.3. Heart and lung transplantation

In heart and lung transplantation, in the first year after transplantation, CMV infection causes substantial morbidity with the most frequent diseases being pneumonia and gastrointestinal disease. It is also associated with an increase in opportunistic infections, bacterial infection and rejection and in the long term with coronary artery disease (Rand et al., 1978; Dummer et al., 1986; Grattan et al., 1989) Table 7.

Table 6
Results of CMV prophylaxis strategies in liver transplantation

Reference	Design	Patient population	Intervention	CMV infection	CMV disease
Snydman et al., 1993	RCT	Any CMV serostatus[a]	CMVIG × 16 weeks ($n = 69$), Placebo ($n = 72$)	CMVIG/placebo 57% 61% P = NS	CMVIG/placebo 19% 31% $P = 0.10$
Saliba et al., 1993	RCT	R+	ACV × 12 weeks ($n = 60$) Control ($n = 60$)	ACV/control 18% 38% $P = 0.01$	ACV/control 19% 31% $P = 0.01$
Martin et al., 1994	RCT	Any CMV serostatus[b]	GCV × 2 weeks then ACV × 10 weeks ($n = 68$) ACV × 12 weeks ($n = 71$)	GCV+ACV/ACV 24% 61% $P < 0.0001$	GCV+ACV/ACV 9% 28% $P < 0.001$
Winston, 1995	RCT	Any CMV serostatus[c]	GCV × 100 days ($n = 124$) ACV × 100 days ($n = 126$)	GCV/ACV 5% 38% $P < 0.0001$	GCV/ACV 0.8% 10% $P = 0.002$
Badley et al., 1997	RCT	Any CMV serostatus[d]	GCV × 14 days then ACV × 106 days ($n = 73$) ACV × 120 days ($n = 74$)	GCV+ACV/ACV 37% 57% $P = 0.001$	GCV+ACV/ACV 11% 23% $P = 0.03$
Dunn et al., 1994	RCT	Any CMV serostatus	GCV+IVIG × 1 wk ($n = 12$) ACV × 12 wks ($n = 14$)	NR	GCV+IVIG/ACV 67% 29%
Green et al., 1994	RCT	Any CMV serostatus	GCV × 2 weeks then ACV × 10 weeks ($n = 10$) GCV × 2 weeks ($n = 19$)	GCV+ACV/GCV 30% 10%	GCV+ACV/GCV 20% 5%
King et al., 1997	RCT	R–D+	GCV × 30 days+ IVIG × 16 weeks ($n = 29$) IVIG × 16 weeks ($n = 27$)	GCV+IVIG/IVIG 55% 41%	GCV+IVIG/IVIG 17% 26%
Nakazato et al., 1993	RCT	Any CMV serostatus	GCV IV then ACV PO × 3 mths ($n = 52$) ACV IV then PO × 3 mths ($n = 52$)	NR	GCV+IVIG ACV+IVIG 3.8% 15% $P < 0.05$
Prian and Koep, 1994	Retro-spective	R+ or D+	GCV × 16 weeks + CMVIG × 16 weeks ($n = 16$) GCV × 2 weeks then ACV × 10 weeks ($n = 12$)	NR	GCV+CMVIG GCV+ACV 0% 50% $P = 0.03$
Ham et al., 1995	Retro-spective	Any CMV serostatus	GCV[e]+ACV+ CMVIG for R–D+ ($n = 15$) GCV+ACV for R+ ($n = 58$) ACV for R–D– ($n = 14$)	R–D+ 40% R+ 24% R–D– 14%	R–D+ 7% R+ 12% R–D– 7%

[a] R–D+: CMVIG = 19 and placebo = 19, CMV infection in 53 versus 53% and CMV-associated disease (including fungal infections) in 37 versus 47%.
[b] Primary CMV infection occurred in 7/14 (50%) of the GCV+ACV group and 11/17 (65%) of ACV alone ($P = 0.2$).
[c] Primary infection occurred in 2/18 (11%) of the GCV group and 42% of the ACV group ($P = 0.06$) with CMV disease in 6 and 16%, respectively ($P = 0.60$).
[d] R–D+ ($n = 12$ and 13): CMV infection in 75 and 83% ($P = 0.27$), CMV disease in 25 and 58% ($P = 0.04$).
[e] GCV for 2 weeks followed by ACV for 6 weeks and CMVIG for 16 weeks.
[f] NS = not statistically significant.

Table 7
Results of CMV prophylaxis strategies in heart and lung transplantation

Reference	Design	Patient population	Intervention	CMV Infection (%)	CMV disease (%)
Aguado et al., 1995	RCT	Heart Tx, R +	GCV × 1 week ($n = 16$) CMVIG × 10 weeks ($n = 15$)	GCV = 81 CMIG = 93	GCV = 6 CMVIG = 40 $P = 0.03$
Merigan et al., 1992	RCT	Heart Tx, R + or R-D +	GCV × 28 days ($n = 76$) Placebo ($n = 73$)	NR	GCV = 16 Placebo = 43 $P < 0.001$
Duncan et al., 1994	RCT	Lung Tx, any CMV serostatus	GCV day 7–21 ACV day 22–90 ($n = 12$) GCV day 7–90 ($n = 13$)	GCV + ACV = 75, GCV = 15 $P < 0.001$	GCV + ACV = 50, GCV = 15 $P = 0.043$

Tx, transplant.

4.3.1. Immune globulin for heart and lung transplant recipients

There is only one RCT in which CMVIG alone is the prophylactic strategy for heart transplant recipients (Aguado et al., 1995). In this trial, CMVIG is compared to GCV for prophylaxis in seropositive CMV recipients. GCV for 2 weeks was more effective than CMVIG for 10 weeks in preventing CMV disease (6 versus 40%, $P = 0.03$). However, adverse effects occurred in 19% of the GCV group (leukopenia and elevated creatinine) but in none of the CMVIG group.

In case series (Eisenmann et al., 1990; Havel et al., 1990; Smyth et al., 1991), the outcome of CMV infection and disease when immune globulin has been used as prophylaxis has been very variable. Eisenmann et al. (1990) followed 23 heart transplant recipients who received CMVIG on days 1, 8, 15, 22, and 42 post-transplant with ACV orally for 6 weeks. Havel et al. (1990) followed 69 heart transplant patients who received CMVIG weekly from day 1 to 28 post-transplant. In these series, only 9 and 21% developed symptomatic CMV disease and only a single case was described as severe. In the report by Smyth et al. (1991) in which 65 heart–lung transplant recipients were followed, the rates of CMV infection ranged from 23 to 39% depending on the R and D serostatus and 21/43 (49%) developed CMV pneumonia. The use of CMVIG did not prevent CMV pneumonia in the R–D + patients who received it.

4.3.2. ACV for heart and lung transplant recipients

Use of ACV alone for CMV prophylaxis has not been reported in clinical trials in heart/lung transplant recipients.

4.3.3. GCV for heart and lung transplant recipients

In a RCT, Merigan et al. (1992) showed that prophylactic GCV significantly reduced the incidence of CMV-associated illness in CMV-seropositive patients. GCV was given from day 1 to 28 post-transplant to heart transplant recipients who were either CMV-seropositive or receiving an organ from a seropositive donor. For the seropositive recipients, the development of CMV disease was reduced from 46 to 9% ($P < 0.01$) and CMV shedding was delayed, so that by day 60, 56% of the placebo had shed CMV compared to 19% of the GCV group ($P < 0.01$). However, for the R–D + patient, there was no clear benefit of GCV prophylaxis for 4 weeks. There were no serious adverse effects of GCV. Elevation in creatinine occurred in 19% of GCV compared with 4% in the placebo group, but the elevations were transient.

In a RCT in lung transplant recipients, the efficacy of a long course (12 weeks) of GCV was compared with a short course (2 weeks) of GCV followed by ACV (for 10 weeks) (Duncan et al., 1994). The longer course of GCV was significantly more effective in preventing CMV disease, includ-

ing reducing the later complications of obliterative bronchiolitis (54 versus 17%, $P < 0.033$). The sample size of this study is too small to assess the benefit for the R−D+ subgroup.

4.3.4. Combination of immune globulin and antiviral therapy for heart and lung transplant recipients

There is very little information on combination prophylaxis in heart/lung transplantation. In one case series (Bailey et al., 1992) ($n = 7$) in which R−D+ lung transplant recipients received IVIG weekly for 2–3 weeks post-transplant and GCV for 2–3 weeks followed by oral ACV, six were viremic and all developed CMV pneumonia. CMV viremia was delayed compared to their historical controls who did not receive this prophylaxis. However, no studies were reported in which GCV was used for a longer course in combination with immune globulin.

4.3.5. Summary for heart and lung transplant recipients

As a single agent, GCV has been shown to be the most effective agent for CMV prophylaxis for heart and lung transplant recipients (see Table 7). It is well tolerated in this patient population. The studies suggest that a longer course of GCV is associated with a longer delay to onset of disease. This strategy is likely to be of greatest benefit for the groups at highest risk of severe disease. To date, there is no convincing evidence in this patient population of the additional benefit of combining CMVIG or IVIG with GCV for prophylaxis. However, optimal management of the R−D+ transplant patient to prevent CMV disease has not been determined.

5. Conclusion

In all transplant settings, GCV is the most effective anti-CMV agent and longer courses of GCV are associated with more effective prevention of infection and longer delay to onset of CMV disease. However, there are several disadvantages to using GCV in this manner due to its toxicity, its inconvenience when given i.v. and its cost. Since one study in liver transplantation has demonstrated the effectiveness of GCV orally, it is likely that this strategy will be studied in other populations. In almost all situations, IVIG alone is not as effective as GCV alone for prevention of CMV infection or disease. But IVIG is beneficial in reducing other complications, such as GVHD post-BMT and GVHD is associated with an increased risk of CMV disease. Therefore, hypothetically, combining IVIG and GCV may provide more effective CMV prophylaxis especially for BMT patients and high-risk solid organ transplant recipients. Unfortunately, the clinical trials reported to date do not provide good evidence to support this.

The use of 'pre-emptive' GCV therapy is an attractive strategy for many post-transplant scenarios because it allows for more selective use of GCV. In settings such as during the use of OKT3, 'risk-adapted' GCV therapy is effective. However, unless a perfect screening tool is developed, there will be cases missed by using a pre-emptive strategy alone. In high-risk groups such as seropositive BMT recipients and R−D+ organ transplant recipients, a combination of prophylaxis and pre-emptive therapy may be most effective. Further studies comparing pre-emptive, risk-adapted and prophylactic strategies are warranted.

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