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Ganciclovir

An Update of its Use in the Prevention of Cytomegalovirus Infection and Disease in Transplant Recipients

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Data Selection

Sources: Medical literature published in any language since July 1998 on Ganciclovir and cytomegalovirus infections in transplant recipients, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'Ganciclovir' and ('cytomegalovirus-infections' or 'cytomegalovirus infection' or 'CMV') and ('transplantation' or 'transplant' or 'transplant recipient'). EMBASE search terms were 'Ganciclovir' or 'BW 759' and ('transplantation' or 'transplant' or 'transplant recipient') and ('cytomegalovirus-infection' or 'cytomegalic-inclusion-body-disease' or 'CMV'). AdisBase search terms were 'Ganciclovir' and ('cytomegalovirus-infections' or 'cytomegalovirus infection' or 'CMV') and ('transplant' or 'transplant recipient'). Searches were last updated 8th June 2001.

Selection: Studies in transplant recipients who received ganciclovir. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Ganciclovir, cytomegalovirus infection, transplantation, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Ganciclovir is a nucleoside guanosine analogue which incorporates ganciclovir triphosphate (the active moiety) into DNA during elongation, thereby inhibiting viral replication.

Comparative studies of pre-emptive and prophylactic ganciclovir therapies in bone marrow transplant (BMT) recipients have shown similar rates of cytomegalovirus (CMV) infection, disease and patient mortality.

Long term prophylaxis with either oral, or sequential intravenous/oral, ganciclovir has shown efficacy in renal allograft recipients, including high risk patients or those receiving antilymphocyte antibody therapy. A preliminary study indicates that ganciclovir is more efficacious than aciclovir in paediatric patients.

Both oral and intravenous prophylactic ganciclovir regimens have shown efficacy compared with no antiviral treatment in lung transplant recipients; initial reports have shown similar efficacy between pre-emptive and prophylactic ganciclovir. Oral ganciclovir monotherapy is as efficacious as sequential intravenous/oral ganciclovir therapy in liver transplant recipients. Pre-emptive treatment was equally as effective as long term ganciclovir prophylaxis in high risk patients.

Ganciclovir prophylaxis for 4 weeks appears ineffective in heart allograft recipients treated with antithymocyte globulin. Long term sequential intravenous/oral ganciclovir therapy has shown greater efficacy in preventing CMV disease than sequential ganciclovir/aciclovir therapy in these patients. Initial reports indicate that pre-emptive therapy may be beneficial in this patient group, although this remains to be determined.

Ganciclovir in therapeutic dosage regimens generally has acceptable tolerability with adverse effects usually of a haematological or neurological nature. Neutropenia, thrombocytopenia and anaemia are the primary dose-limiting toxicities associated with ganciclovir therapy. Overall, neutropenia occurs less frequently with administration of oral ganciclovir than with intravenous ganciclovir. Monitoring of renal function is recommended as serum creatinine levels may rise during ganciclovir therapy. In addition, ganciclovir prophylaxis appears more cost effective than the majority of other currently available therapies for CMV, with oral ganciclovir more cost effective than intravenous ganciclovir.

In conclusion, it is unlikely that a single strategy will be able to be applied to all transplant patients for the prevention of CMV disease. An optimal strategy will probably be a risk-adapted approach. Prophylactic treatment with ganciclovir appears the best strategy to implement in high risk patients; oral ganciclovir formulations may be best employed where lower toxicity is required. Pre-emptive treatment with ganciclovir appears most efficacious in patients identified as lower risk or, in the case of BMT recipients, where lower toxicity may be desirable. Ganciclovir remains an important therapeutic option for the prevention and treatment of CMV disease in transplant recipients.

Pharmacodynamic Properties

Ganciclovir, a nucleoside guanosine analogue, inhibits viral replication through incorporation of the active moiety ganciclovir triphosphate into the growing chain of viral DNA. *In vitro*, median ganciclovir concentrations of between 0.1 and 1.6 mg/L are sufficient to inhibit cytomegalovirus (CMV) replication by 50% (IC_{50}). Synergistic activity against CMV has been demonstrated *in vitro* and *in vivo* with ganciclovir in combination with a variety of antivirals and immunosuppressants.

Ganciclovir-resistant CMV isolates have been both selected *in vitro* and recovered *in vivo* from immunocompromised patients treated with antiviral agents and are associated with UL97 and UL54 mutations. Resistance to ganciclovir has been reported in 5.2 and 2.1% of allograft recipients in 2 retrospective analyses. Resistance was associated with a greater total dose of ganciclovir, a higher CMV viral load, a greater number of pneumonitis episodes and a longer period of time prior to detection in lung transplant patients. Resistance to ganciclovir occurred more frequently in donor seropositive/recipient seronegative (D+/R–) patients than in seropositive recipients, and in kidney and pancreas, or pancreas alone allograft recipients than in kidney or liver transplant recipients. In addition, ganciclovir-resistant isolates have been identified in bone marrow transplant (BMT) recipients who had been treated with intravenous ganciclovir after receiving aciclovir prophylaxis.

Pharmacokinetic Properties

Both oral and intravenous ganciclovir demonstrate linear pharmacokinetics. Mean maximum plasma ganciclovir concentrations of ≈0.8 mg/L and mean area under the plasma concentration-time curve values of ≈10.9 mg/L • h were seen following oral administration of ganciclovir 1000mg. The estimated oral bioavailability of ganciclovir is ≈7% in both adult and paediatric patients. Steady-state drug trough concentrations following administration of oral ganciclovir (1000mg 3 times daily) were at least within the IC_{50} range.

Ganciclovir shows minimal binding to plasma proteins. Both oral and intravenous ganciclovir are principally excreted via the kidneys with a terminal elimination half-life of ≈6.0 to 9.7 hours. Renal dysfunction reduces elimination of ganciclovir and dosage reductions are required in these patients.

Therapeutic Use

Allogeneic bone marrow transplantation: Intravenous ganciclovir 5 mg/kg

prophylaxis administered 5 times weekly was more efficacious than a 3-times-weekly regimen, with significantly lower rates of CMV infection, CMV disease and CMV-related mortality. Similar rates of CMV infection, disease and patient mortality have been observed with prophylactic (all patients) and pre-emptive (initiated on detection of asymptomatic CMV infection) treatments in comparative studies. The use of intravenous aciclovir prior to transplantation did not affect these outcomes. Pre-emptive therapy with intravenous ganciclovir (5 mg/kg twice daily) has shown equivalent efficacy to that with intravenous foscarnet (60 to 90 mg/kg twice daily) with respect to the incidence of CMV disease and CMV-related patient mortality in randomised comparisons. D+ and/or R+ patients treated pre-emptively had similar CMV infection and mortality outcomes to D–/R– patients receiving no antiviral treatment, although rates of CMV disease were higher.

Kidney transplantation: Long term (3-month) prophylaxis with either oral (1500 to 3000mg daily), or sequential intravenous/oral ganciclovir (5 mg/kg/day, then 3000 mg/day) has shown greater efficacy against CMV infection than long term oral aciclovir 2400mg daily, short term intravenous ganciclovir or no antiviral prophylaxis in nonblind comparative studies. Rates of CMV disease were lower in patients who received prolonged ganciclovir prophylaxis than in patients who did not, even in the subgroups which received antilymphocyte antibody (ALA) therapy. Similarly, rates of acute rejection were lower, although this may be attributable to differences in baseline immunosuppression. Prolonged oral ganciclovir was more effective than no antiviral prophylaxis over a range of dosages in donor and/or recipient seropositive patients; higher dosages in patients receiving ALA therapy were also effective. Monoclonal antibody immunosuppression resulted in significantly higher rates of CMV infection in those receiving intravenous ganciclovir therapy, although no differences in tissue-invasive CMV disease or 12-month survival were seen.

Combination oral ganciclovir/aciclovir prophylaxis was more effective than intravenous immunoglobulin/aciclovir at preventing CMV disease in a retrospective analysis. Higher rates of CMV disease were observed in paediatric patients receiving aciclovir 1500 than ganciclovir 1800 mg/day in a small retrospective trial. Results of a nonblind study of pre-emptive therapy suggest similar efficacy between oral aciclovir 1200mg daily and oral ganciclovir 1000mg daily, although tissue-invasive CMV disease was only confirmed in patients receiving antirejection therapy. Identified risk factors for recurrent episodes of CMV were having diabetes mellitus, use of acute rejection treatment, receiving a cadaver organ and receiving a simultaneous kidney-pancreas transplant. A greater number of D+/R– patients than those with other serologies experienced episodes of CMV recurrence.

Lung transplantation: Long term oral (1000mg 3 times daily) and intravenous ganciclovir (5 mg/kg twice daily) prophylactic regimens have shown significant reductions in the incidence of CMV disease compared with no antiviral treatment. Patients receiving once daily ganciclovir prophylaxis had lower rates of 12-month mortality than patients receiving ganciclovir 3 times weekly, although this was not attributable to a reduction in CMV-related disease. A preliminary study demonstrated equivalent efficacy between pre-emptive treatment and prophylaxis in D–/R+ and D+/R– patients. An initial investigation employing deferred treatment reported a lower incidence of CMV disease, and no CMV

disease in seropositive patients, compared with a group receiving no antiviral prophylaxis.

Liver transplantation: Prolonged administration of oral ganciclovir (1000mg 3 times daily) was effective in significantly reducing CMV infection and disease in a double-blind, placebo-controlled study. A preliminary retrospective report indicated that prolonged oral ganciclovir prophylaxis was significantly more efficacious than oral aciclovir (800mg twice daily) in D+/R+ and D–/R+ patients, but not in D+/R– patients. Similar rates of CMV infection and disease were observed in patients receiving prophylaxis with either sequential intravenous ganciclovir/oral aciclovir, or oral ganciclovir monotherapy followed by oral aciclovir. Pre-emptive treatment was equally as efficacious as long term ganciclovir prophylaxis in D+/R– patients. Fewer patients (including high risk patients) subsequently developed CMV infection and disease following pre-emptive treatment with oral ganciclovir than after placebo in a double-blind, placebo-controlled trial. Similar rates of CMV infection and disease were observed in patients receiving pre-emptive treatment with either oral or intravenous ganciclovir in a nonblind comparison.

Heart transplantation: Prophylaxis with intravenous ganciclovir 5 mg/kg twice daily for 4 weeks showed no benefit on CMV morbidity and mortality in high risk patients receiving antithymocyte globulin (ATG) compared with patients receiving no antiviral prophylaxis. Long term sequential intravenous/oral ganciclovir has shown greater efficacy in preventing CMV disease than sequential intravenous ganciclovir/oral aciclovir, and similar efficacy to intravenous CMVIg/oral aciclovir prophylaxis. Data regarding the use of pre-emptive treatment in heart transplantation are still limited. Preliminary data suggest that pre-emptive treatment may reduce the incidence of CMV disease compared with patients receiving ganciclovir prophylaxis.

Tolerability

Adverse effects associated with ganciclovir therapy are generally of a haematological nature. Dosage reduction is most commonly indicated for neutropenia, thrombocytopenia and anaemia. BMT recipients are especially susceptible to neutropenia; neutropenia usually occurs early in treatment and is generally reversible. Prolonged administration of intravenous ganciclovir in BMT recipients is associated with an increase in opportunistic infections.

No significant differences in the incidences of thrombocytopenia and leucopenia or impaired renal function were observed between patients receiving intravenous ganciclovir and those receiving intravenous foscarnet. Severe neutropenia was observed significantly less often in patients treated with foscarnet than in those receiving ganciclovir.

Elevated serum creatinine levels have been observed in patients receiving intravenous ganciclovir in controlled clinical trials; renal function monitoring is recommended. Neurological adverse effects (e.g. headache, confusion) have also been reported in transplant patients.

Dosage and Administration

Ganciclovir is available for use in the prevention and treatment of CMV disease in bone marrow and solid organ transplant recipients. The recommended dosage regimen for prophylaxis with oral ganciclovir for patients with normal renal function is 1000mg 3 times daily with food. Intravenous ganciclovir (5 mg/kg) should be administered every 12 hours for 7 to 14 days, followed by either 5 mg/kg once daily 7 days per week or 6 mg/kg once daily 5 days per week.

Dosages of ganciclovir should be adjusted according to renal dysfunction and

tolerability and the drug is contraindicated in patients with an absolute neutrophil count of <500/μl, or a platelet count of $<25 \times 10^3$/μl. Caution is also advised in patients receiving concomitant therapy with cyclosporin, amphotericin B or other nephrotoxic drugs.

Pharmacoeconomic Considerations

Overall, prophylaxis with ganciclovir (both intravenous and oral) or oral valaciclovir is cost effective compared with other currently available therapies for the prevention of CMV infection and disease in solid organ transplant recipients. Furthermore, prophylaxis with oral ganciclovir appears more cost effective than prophylaxis with intravenous ganciclovir.

Ganciclovir, a nucleoside guanosine analogue with therapeutic activity against human cytomegalovirus (CMV) infection, was first reviewed in *Drugs* in 1990,[1] and an update was subsequently published in 1994.[2] A further update of its use in allogeneic bone marrow transplantation (BMT) and solid organ transplantation was published in 1998.[3]

Most studies published since the last review in *Drugs*[3] have focused on strategies to prevent CMV infection, rather than on treatment of symptomatic disease, and this review takes a similar approach.

1. Introduction

CMV is a major cause of morbidity and mortality in solid organ transplantation, with event rates in untreated patients ranging between 19 and 90% for CMV infection and 26 and 90% for CMV disease.[4] An especially high incidence of CMV infection is observed in allogeneic BMT recipients with reactivation occurring in almost all patients seropositive prior to transplantation, and in approximately 30% of donor seropositive/recipient seronegative (D+/R–) patients.[5]

The risk of developing CMV disease in solid organ transplant patients is comparatively low following kidney transplantation, higher after liver and heart transplantation, and is highest in lung transplant patients.[6] CMV disease usually occurs at the site of transplant following solid organ transplantation, except in renal allograft patients where overt CMV invasion of the allograft is rarely seen.[6]

2. Overview of Pharmacodynamic Properties

The pharmacodynamic properties of ganciclovir have been reviewed extensively elsewhere.[3] This section provides an overview of the *in vitro* and *in vivo* properties of the drug, with emphasis on recently published reports of ganciclovir resistance.

2.1 Mechanism of Action

Ganciclovir, a nucleoside guanosine analogue, is preferentially phosphorylated to ganciclovir monophosphate in infected cells (in a rate-limiting step) by a protein encoded with the UL97 open reading frame of human CMV. It is then metabolised to ganciclovir di- and triphosphate through the action of host cellular kinases.[7]

The active drug inhibits viral replication by competing with deoxyguanosine triphosphate as a substrate for the enzyme DNA polymerase. The incorporation of ganciclovir triphosphate into the growing chain of viral DNA slows extension, thereby inhibiting viral replication.[7,8]

2.2 Antiviral Activity

Ganciclovir shows potent antiviral activity against human CMV. The drug has a similar mechanism of action to that of aciclovir, but is approximately 26 times more potent against CMV *in vitro*, according to the mean concentration required to achieve 50% viral inhibition (IC_{50}).[3] Intracellular concentrations of ganciclovir triphosphate in CMV-infected cells are approximately 10-fold higher than those produced by uninfected cells. Similarly,

ganciclovir triphosphate concentrations are more than 10-fold higher than concentrations of aciclovir triphosphate achieved under similar conditions.[9]

CMV replication is inhibited (IC_{50}) *in vitro* at median concentrations of between 0.1 and 1.6 mg/L.[8] Substantially higher concentrations of ganciclovir are required to inhibit proliferation of uninfected host cells. Bone marrow cells, however, are especially sensitive to ganciclovir.[9]

As discussed previously, ganciclovir has synergistic activity against CMV both *in vitro* and *in vivo* in combination with foscarnet, cidofovir, mycophenolate mofetil, immunotoxin or anti-CMV antibodies (mono- or polyclonal).[3] Several studies also established the efficacy of ganciclovir in animal models of CMV infection, with moderate synergistic activity observed between ganciclovir and CMV hyperimmune serum.[3]

2.3 Other Effects

Earlier data from several *in vitro* and *in vivo* studies suggested that ganciclovir inhibits immune responses associated with CMV infection and/or graft rejection. Ganciclovir also inhibits smooth muscle proliferation and CMV-associated graft arteriosclerosis. Prophylaxis with ganciclovir in bone marrow recipients is associated with a delay in reconstitution of cellular immune responses to CMV.[3]

2.4 Viral Resistance to Ganciclovir

Ganciclovir-resistant CMV isolates have been both selected *in vitro* and recovered *in vivo* from immunocompromised patients treated with antiviral agents.[10] Clinical CMV strains have been associated with mutations in the UL97 (usually at codons 460, 594 and 595), DNA polymerase, or both viral genes. The functional consequence of UL97 mutations is an impaired phosphorylation of ganciclovir in virus-infected cells, resulting in a lack of synthesis of the active metabolite ganciclovir triphosphate.[10]

CMV strains containing only UL97 mutations are resistant to ganciclovir, but susceptible to foscarnet and cidofovir. CMV strains with some UL54 mutations are cross-resistant to ganciclovir and cidofovir, and CMV strains containing UL97 and UL54 mutations (double-mutant strains) are highly resistant to ganciclovir.[10]

Previously, ganciclovir resistance was widely reported in patients with AIDS, with only anecdotal published evidence documenting the existence of resistance in transplant recipients. However, recently, 2 retrospective analyses of ganciclovir resistance in transplant patients (the first in lung and the second in liver, kidney, kidney and pancreas and pancreas transplant patients) have been reported.[11,12]

In the first,[11] 18 (5.2%) of 348 lung transplant recipients receiving intravenous pre-emptive therapy (5 mg/kg twice daily for 8 weeks then 4 times daily for 4 weeks then 3 times daily for 4 weeks) exhibited some degree of ganciclovir resistance. Retrospective analysis matched identified patients with ganciclovir-resistant CMV (n = 18) with non-resistant controls (n = 18). Patients with resistant CMV had received a greater total dose of antithymocyte globulin (ATG) [p = 0.03] and ganciclovir (p = 0.005), had been treated for a longer period of time prior to detection (p = 0.005), had a higher number of CMV-positive blood cultures (p = 0.02), and had a greater number of pneumonitis episodes (p = 0.02) than controls.[11]

In the second analysis,[12] of 240 patients receiving liver, kidney, kidney and pancreas, or pancreas transplants, 2.1% developed ganciclovir-resistant CMV after prolonged exposure to oral ganciclovir (1000mg 3 times daily for 100 days). All patients with resistant CMV were D+/R– [p = 0.002, compared with seropositive recipients]. The overall occurrence of viral resistance in D+/R– patients was 7%. Of these, ganciclovir-resistant CMV appeared more frequently in kidney and pancreas, or pancreas alone allograft recipients than either kidney or liver transplant recipients (p = 0.005). The authors proposed that this may have been due to immunosuppression regimens of greater intensity used in these patients.[12]

Moreover, ganciclovir-resistant CMV isolates were identified in 3 of 8 BMT recipients with active CMV infection treated for a mean 69 days with intravenous ganciclovir (5 mg/kg every 12 hours for 14 days, then 5 mg/kg every 5 days out of 7 for 4 weeks) after receiving prophylaxis with aciclovir (10 mg/kg intravenously every 8 hours up to 10 days prior to transplantation, then 800mg orally 5 times daily to day 100).[13]

3. Overview of Pharmacokinetic Properties

Detailed information on the pharmacokinetics of ganciclovir is available in previous reviews.[2,3] This section provides a brief summary of the pharmacokinetics of intravenous ganciclovir, and concentrates on newly available information on the pharmacokinetics of orally administered ganciclovir in transplant patients (summarised in table I).

3.1 Absorption and Distribution

Mean peak drug concentrations (C_{max}) of both oral and intravenous ganciclovir show linear pharmacokinetics over the single dose ranges 1000 to 6000mg and 1 to 5 mg/kg, respectively.[3,14]

A single dose of oral ganciclovir (1000mg) resulted in a C_{max} of 0.8 mg/L approximately 6 hours after administration in seropositive bone marrow recipients.[14] A mean plasma area under the concentration-time curve (AUC) value of 10.9 mg/L • h was reported which was approximately one-third that observed with intravenous ganciclovir 200mg (29.2 mg/L • h).[14]

The estimated oral bioavailability of ganciclovir is ≈7% in adult transplant recipients.[14-16] Absorption is increased in patients with HIV infection when ganciclovir is administered with food.[14]

It is currently unclear whether trough or peak plasma ganciclovir concentrations are more important for antiviral activity. However, recommended trough concentrations (C_{min}) of between 0.2 and 0.6 mg/L compare with an IC_{50} for CMV ranging from 0.26 to 1.28 mg/L.[18] Steady-state ganciclovir C_{min} and C_{max} following administration of oral ganciclovir (1000mg 3 times daily) in CMV-seropositive BMT recipients were at least within the IC_{50} range and were 1.1 and 1.6 mg/L, respectively.[14] The steady-state volume of distribution (V_{ss}) of ganciclovir after intravenous administration was 50.2L.[14]

Following intravenous administration, ganciclovir is minimally bound to plasma proteins (1 to 2%) over ganciclovir concentrations of 0.5 to 51 mg/L.[17]

3.2 Elimination

The elimination half-lives ($t_{½}$) following administration of oral and intravenous ganciclovir are approximately 7.9 to 9.7 hours[14,15] and 6.0 hours, respectively.[14]

Ganciclovir is primarily excreted via glomerular filtration and active tubular secretion; therefore, impaired renal function reduces elimination of the drug necessitating dosage reduction (see section 6).[15] Total plasma clearance in patients receiving oral ganciclovir is 0.1 L/h/kg[15] and approximately 0.2 L/h/kg following administration of intravenous ganciclovir.[17]

87% of oral ganciclovir (3000mg in 3 divided doses) was recovered in the urine of 28 liver allograft recipients.[16]

3.3 Special Patient Groups

Increased systemic exposure to ganciclovir has been observed in patients with impaired renal function.[15] In addition, mean maximum plasma concentrations and AUC of ganciclovir following oral administration (1000mg 3 times daily) in lung transplant patients (n = 12) with cystic fibrosis were 4.8 mg/L and 35.4 mg • 8h/L, respectively.[19]

The median oral bioavailability of ganciclovir in paediatric renal transplant patients (n = 14; age range 7 to 18 years) was 7.8%.[18] C_{min} values of between 0.28 and 6.7 mg/L were achieved with dosages of 7.8 to 52 mg/kg/day. From this the authors concluded that a dosage of 100 mg/kg daily (in 3 divided doses) was required to achieve a C_{min} of 1 mg/L.[18]

C_{max} values following a single dose of either 40 or 20 mg/kg oral ganciclovir in paediatric patients

Table I. Summary of the main pharmacokinetic properties of ganciclovir (GCV). Data are from single-dose studies conducted in adult seropositive bone marrow,[14] renal[15] and liver[16] transplant recipients

Oral GCV
Linear pharmacokinetics over the dose range 1000 to 6000mg[14]
Bioavailability ≈7%[14-16]
Increased absorption from gastrointestinal tract when taken with food in patients with HIV infection[17]
C_{max} ≈0.8 mg/L with t_{max} ≈6 hours after 1000mg dose[14]
Plasma clearance 0.1 L/h/kg[15]
Plasma $t_{1/2}$ of 7.9 to 9.7h[14,15] 87% of 1000mg dose recovered from urine[16]
Intravenous GCV
Linear pharmacokinetics over the dose range 1 to 5 mg/kg[3]
C_{max} ≈6 mg/L after 1.1 hours (200mg GCV)[14]
≈1 to 2% bound to plasma proteins[17]
Plasma $t_{1/2}$ of 6h[14]
Plasma clearance 0.2 L/h/kg[17]
V_{ss} = 50.2L[14]

C_{max} = peak plasma concentration; **t_{max}** = time to reach C_{max}; **$t_{1/2}$** = elimination half-life; **V_{ss}** = volume of distribution at steady-state.

who had received a liver transplant (n = 9; age range 6 months to 12 years) were 3.6 to 6.9 mg/L and 0.38 to 4.75 mg/L, respectively. t_{max} (time to C_{max}) occurred 1 to 3 hours after administration.[20]

4. Therapeutic Use

Many strategies have been employed in an attempt to prevent and treat CMV infection and/or disease; however, the most common are:

- prophylaxis of all patients undergoing transplantation
- targeted prophylaxis (i.e. prophylaxis is administered only to those patients considered at high risk for infection)
- pre-emptive treatment (i.e. antiviral therapy is initiated upon detection of asymptomatic CMV infection during regular monitoring)
- deferred treatment (i.e. treatment is withheld until CMV disease is evident).

There are several techniques available for the detection of CMV as part of pre-emptive treatment, of which the CMV antigen (pp65) assay or polymerase chain reaction (PCR) are most sensitive to lower viral loads.

Primary infection is usually asymptomatic; reactivation and development of CMV-related disease are generally associated with immunosuppressive conditions, caused by either disease or drug administration in transplant recipients.[21]

Many of the studies in this section are retrospective analyses which have compared CMV morbidity and mortality outcomes after a change in regimens in a transplant programme with those associated with the previously used regimen. Although there have been few well-controlled trials since the previous review,[3] general experience in the area has expanded. Recent studies of ganciclovir and CMV disease in transplant recipients have investigated the effect of various dosages and regimens of ganciclovir (especially oral ganciclovir) on CMV status in high risk (D+/R–) or intermediate risk (D–/R+, D+/R+) patients. Emphasis has also shifted towards identification of those aetiological factors contributing to CMV reactivation, and the potential of ganciclovir in preventing recurrent episodes in renal transplant patients.

Previously, the initiation of antiviral therapy following detection of CMV infection during routine monitoring was referred to as 'early treatment'. For the purposes of this review, this is termed 'pre-emptive' treatment.

4.1 Allogeneic Bone Marrow Transplantation

The effectiveness of prophylactic or pre-emptive treatment with ganciclovir in preventing CMV was established at the time of the previous review and was supported by evidence from several non-comparative trials.[3] Both approaches appeared to reduce the incidence of CMV infection and/or disease, but had little effect on patient mortality. However, questions remain as to which dosage and schedule is optimally effective against CMV whilst limiting adverse effects.

4.1.1 Prophylactic and Pre-Emptive Treatments

A retrospective study found significant differences between 2 regimens of ganciclovir prophylaxis. 41% of patients receiving ganciclovir (5 mg/

kg intravenously) 3 times per week developed CMV infection at 100 days compared with 21% of patients receiving the same dosage of ganciclovir 5 times weekly (p = 0.005). Similarly, rates of CMV disease were 16 and 4%, respectively (p = 0.004).[22] Overall, mortality did not differ between the 2 groups (66 *vs* 76%; Kaplan-Meier estimate; p = 0.3). However, CMV-related mortality was significantly higher in the 3-times-weekly group (12%) than the 5-times-weekly group (1.5%, p = 0.003).[22]

Ganciclovir prophylaxis (5 mg/kg intravenously twice daily 8 days prior to and from 30 days post-transplantation) may be effective in preventing CMV pneumonia in the early transplant period;[23,24] however, late-onset CMV pneumonia (>100 days) is still a major cause of morbidity and mortality, occurring primarily in patients with chronic graft-versus-host-disease (GVHD) or those who received T-cell–depleted transplants.[24]

Results from clinical trials of intravenous ganciclovir as pre-emptive treatment are shown in table II.

Previously, a double-blind comparison of pre-emptive and prophylactic treatments showed significantly reduced rates of CMV disease in BMT patients receiving ganciclovir prophylaxis at day 100, but not at day 180.[25] Moreover, administration of aciclovir prior to transplantation (followed by ganciclovir prophylaxis at engraftment) did not improve CMV outcomes when compared with the results of the double-blind trial in a subsequent analysis.[27] More recently, a retrospective comparative study by Stocchi et al.[26] in consecutive volunteer-unrelated donors reported no significant differences between rates of CMV disease or total survival at 12 months with pre-emptive or prophylactic therapy, although the probability of CMV infection at 12 months was significantly higher and there was a tendency for more patients to develop CMV disease in the group receiving pre-emptive therapy (table II). Randomised nonblind comparisons of ganciclovir with foscarnet (1 in abstract form[28]) have shown similar efficacy between the 2 drugs given as pre-emptive treatments (table II).[28,29]

CMV morbidity and mortality outcomes have been investigated in a prospective study comparing consecutive D+ and/or R+ patients receiving pre-emptive intravenous ganciclovir treatment with D–/R– patients receiving no antiviral treatment.[31] Of D+ and/or R+ patients who received pre-emptive treatment with ganciclovir (n = 16), a significantly greater number developed CMV disease (11%) than D–/R– patients who received no antiviral therapy (0%; p < 0.05). CMV-related mortality at 36 months did not differ significantly for D+ and/or R+ versus seronegative patients (5 *vs* 0%, respectively) [table II].

A retrospective study examined the efficacy of pre-emptive therapy in seropositive (n = 80) and seronegative (n = 35) recipients from HLA-identical sibling donors (table II).[30] 30 seropositive patients subsequently received treatment with ganciclovir. There were no significant differences between the groups in CMV-related mortality at 3 years; however, overall survival at 5 years was significantly lower in the seropositive cohort (40%) than the seronegative cohort (64%; p = 0.01).[30]

4.2 Kidney Transplantation

At the time of the previous review,[3] the use of targeted prophylaxis with oral or intravenous ganciclovir had been evaluated in several randomised comparative studies. Generally, these indicated that targeted prophylaxis with ganciclovir was effective in reducing the incidence of CMV infection and/or disease in immunosuppressed renal transplant recipients.[32-35] Additionally, results from the few studies employing pre-emptive or deferred ganciclovir therapy were reported and overall these were encouraging in higher risk patients.[36,37]

4.2.1 Prophylactic Treatment

Differing regimens of long term prophylactic therapy (usually 12 weeks) in patients selected as at high or intermediate risk for CMV infection [some also receiving antilymphocyte antibody (ALA) therapy] have been compared in recent in-

Table II. Efficacy of intravenously administered ganciclovir (GCV) as pre-emptive (PE) treatment for cytomegalovirus (CMV) infection and disease in allogeneic bone marrow transplant recipients: data from comparative studies. All patients received GCV after detection of asymptomatic CMV infection during routine monitoring after transplantation (i.e. pre-emptively)

Reference (design)	CMV serology	Method of CMV detection	Treatment regimen	No. of pts	Time of main assessment (days)	Results (% of pts) [at main assessment unless stated otherwise]		
						CMV infection	CMV disease	CMV-related mortality
PE *vs* prophylactic (PT) treatments								
Boeckh et al.[a][25] (r, db, pc)	R+	pp65	PL; GCV 5 mg/kg IV administered nb for 7 days, then od for 3wk if Ag+ detected (PE)	114	100	79	14.1 [20.2 at 400 days]	7.0 [11.4 at 400 days]
			GCV 5 mg/kg IV bid for 5 days then od for 6 days/wk for 95 days; GCV administered nb if Ag+ detected (PT)	112		41	2.7* [16.1 at 400 days]	3.6 [11.6 at 400 days]
Stocchi et al.[b][26] (nb, ret)	D+ and/ or R+	DEAFF	GCV 5 mg/kg IV bid for 2wk then od for 5 days/wk for 120+ days (PE)	27	120	70 [73.8* at 12mo]	[64 at 12mo]	[11.1 at 12mo]
			GCV 5 mg/kg/day IV 5 days/wk for 120+ days (PT)	22		45 [53.1 at 12mo]	[30 at 12mo]	[13.6 at 12mo]
Boeckh et al.[27] (ret)	R+	pp65	GCV 5 mg/kg IV for 7 days for minimum 3wk (PE)	114[c]	100	NR	21	[6.3 at 2y]
			GCV 5 mg/kg IV bid at engraftment for 1wk followed by 5 mg/kg/day (min 3wks) to day 100 (PT)	112[c]		NR	16	[12.3 at 2y]
			ACV 500 mg/m^2 every 8h IV from day 5 before transplant until engraftment then GCV 5 mg/kg IV bid for 5 days and 5 mg/kg 6 to 7 days/wk until day 100 (PT)	133		NR	13	[6.0 at 2y]
GCV *vs* FOS (both PE)								
Reusser et al. [28] [abs] (r, mc, nb)	NR	PCR or pp65	GCV 5 mg/kg IV bid for 2wk	103	180	NR	5	NR
			FOS 60 mg/kg IV bid for 2wk	110		NR	5	NR
Moretti et al.[29] (r, nb)	All	pp65	GCV 5 mg/kg IV bid for 15 days	19	100+	NR	11	[10.5 at 12mo]
			FOS 90 mg/kg IV bid for 15 days	20		NR	5	[5.0 at 12mo]
PE GCV *vs* no antiviral therapy								
Broers et al.[30] (nb, ret)	D+ and/or R+	pp65	GCV 5 mg/kg IV bid until negative test (median 10 days)	80[d]	150	NR	NR	[2.5 at 36mo]
	D–/R–		No antiviral therapy	35		NR	NR	[0 at 36mo]
Reddy et al.[31] (nb)	D+ and/or R+	BAL	GCV 5 mg/kg IV bid for 14 days (PE)	55[e]		30	11*	[5.5 at 36mo]
	D–/R–		No antiviral therapy	43		0	0	[0 at 36mo]

a All patients were monitored weekly for CMV infection; if high grade Ag+ (≥3 positive cells in 2 slides) was detected or there was a positive blood culture, pts received IV GCV 5 mg/kg bid for 7 days then od for 3wk or until 6 days after cessation of Ag+/viraemia. Viraemia was the first sign of infection in only 1 patient.

b Patients had chronic myelogenous leukaemia and received transplants from unrelated donors.

c Patients are the same as those from the randomised trial of Boeckh et al.[25] Patients in the ACV-treated group received transplants before the start of the randomised trial.

d Only 30 patients received GCV.

e Only 16 patients received GCV.

abs = abstract; **ACV** = aciclovir; **Ag+** = positive antigenaemia; **BAL** = bronchoalveolar lavage; **bid** = twice daily; **D** = donor; **db** =double-blind; **DEAFF** = detection of early antigen fluorescent foci; **FOS** = foscarnet; **IV** = intravenous; **mc** = multicentre; **nb** = nonblind; **NR** = not reported; **od** = once daily; **pc** = placebo-controlled; **PCR** = polymerase chain reaction; **PL** = placebo; **pp65** = pp65 antigenaemia; **pts** = patients; **R** = recipient; **r** = randomised; **ret** = retrospective analysis; * $p < 0.05$ *vs* comparator.

vestigations. Patients in these trials were assigned to one of 2 different drug regimens, or were compared with a low risk group (D–/R–) receiving no antiviral prophylaxis (table III).

Studies with Long Term Ganciclovir

Although well-designed studies are lacking, there are indications that long term prophylaxis with either oral or sequential intravenous/oral ganciclovir regimens is more effective in preventing CMV infection than long term oral aciclovir[38] (fig. 1), short term intravenous ganciclovir administered only during antirejection therapy[39] or no antiviral prophylaxis[41](table III).

A significant benefit on CMV disease outcomes at 12 months was observed in a prospectively designed nonblind clinical trial comparing D+/R– patients receiving prolonged sequential intravenous/oral ganciclovir therapy with D+/R– patients who received intravenous ganciclovir only during antirejection therapy with mono- or polyclonal antibodies (table III).[39] Furthermore, this difference remained when only patients with CMV disease from both groups who did not receive ALA therapy were considered (23.1 *vs* 70%, $p < 0.001$). Acute rejection also occurred less often in those treated with ganciclovir (41.9%) than those who were not (71.4%, $p < 0.05$), although this may be attributable to differences in baseline immunosuppression.[39]

Lower rates of CMV infection were observed in patients who had been administered oral ganciclovir (either 500 or 750mg twice daily) over a 3-month treatment period than in patients who had received no antiviral prophylaxis. No difference in efficacy was observed between the 2 dosages.[41] Moreover, patients receiving long term prophylaxis with lower dosages of oral ganciclovir (either 250 or 500mg twice daily), and no ALA therapy, showed no significant difference in rates of infection between the 2 groups.[40]

Additionally, the incidence of CMV disease was significantly higher in a group of renal allograft patients receiving intravenous ganciclovir 5 mg/kg/day prophylaxis who also received predominantly monoclonal antibody immunosuppression, than in a group who were treated with ganciclovir and a less intensive immunosuppressive regimen (28 *vs* 7%; $p < 0.05$). Nevertheless, no significant differences were observed in the incidence of tissue-invasive CMV disease (5 *vs* 0%) or overall survival at 12 months (95 *vs* 97%).[43]

Comparison with Immune Globulin

A retrospective analysis compared CMV morbidity and mortality outcomes in D+ and/or R+ patients who received sequential prophylactic therapy with intravenous ganciclovir and long term oral aciclovir, and historical controls (also D+ and/or R+) treated with intravenous immune globulin (IVIG) followed by long term oral aciclovir. Similar rates of CMV disease and 12-month mortality were observed between the 2 groups (table III).[42] However, ganciclovir/aciclovir treatment was more effective in preventing CMV disease in D+/R– patients than was IVIG/aciclovir ($p < 0.05$).[42]

In Paediatric Patients

The results of a single retrospective comparative study of prophylaxis in paediatric renal allograft patients (ages not specified) has been reported in abstract form.[44] Patients received either oral ganciclovir (1800mg daily in 3 divided doses; n = 17) with basiliximab induction, or oral aciclovir (1500mg daily in 3 divided doses; n = 13) with ALA therapy. The incidence of CMV disease at 6 months in the 2 groups was 5 and 46%, respectively (p-value not given).[44]

4.2.2 Pre-Emptive Treatment

Few studies have investigated the efficacy of pre-emptive treatment for the prevention and management of CMV in kidney transplant patients. At the time of the last review, it appeared that the occurrence of CMV infection did not affect long term survival after renal transplantation if a short course of intravenous ganciclovir was given when viraemia was detected.[3] Since the previous review only 1 study looking at pre-emptive ganciclovir treatment in seropositive renal and liver transplant patients receiving monoclonal antibodies as either induction or antirejection therapy has been published.[45] In this nonblind comparative study, patients re-

Table III. Efficacy of ganciclovir (GCV) as targeted prophylaxis for cytomegalovirus (CMV) infection in renal transplant recipients in nonblind comparative studies. Some patients received antilymphocyte antibody (ALA) therapy

Reference (design)	CMV serology	ALA therapy	Antiviral treatment regimen	No. of pts	Time of main assessment (mo)	Results (% of pts) [at main assessment unless otherwise stated]		
						CMV infection	CMV disease	mortality
Comparison of long term oral GCV with ACV								
Flechner et al.[a][38] (r)	D+/R– D+/R+ D–/R+	OKT-3 [Ind]	GCV 1000mg PO tid 3mo	40	6	3** [0* in D+/R–]	3 [0* in D+/R–]	NR
	D+/R– D+/R+ D-/R+		ACV 800mg PO qid 3mo	39		38 [54.1 in D+/R–]	23 [71.4 in D+/R–]	NR
	D–/R–		No antiviral prophylaxis	22		5	0	NR
Comparison of long term sequential GCV								
Kletzmayr et al.[39] (nb)	D+/R–	No ALA[b]	GCV 5 mg/kg/day IV for 2 to 3wk; then GCV 3 g/day PO for 3mo	31	12	45*	29*	3
			No antiviral prophylaxis[c]	28		75	60	11
Comparison of long term oral GCV								
Yang et al.[40] (nb, con)	D+/R– D+/R+ D–/R+	No ALA	GCV 500mg PO bid for 3mo	20	6	0	NR	NR
			GCV 250mg PO bid for 3mo	20		5	NR	NR
Ahsan et al.[41] (r, nb)	D+/R– D+/R+ D–/R+	OKT-3[d]	GCV 750mg PO bid 3mo	15	6	7*	NR	0
			GCV 500mg PO bid 3mo	20		0*	NR	0
			No antiviral prophylaxis	16		38	NR	6
Comparison of GCV with IVIG								
Walton et al.[42] (ret)	D+/R– D+/R+ D–/R+	ATG or OKT-3 [Ind]	GCV 2.5 mg/kg/day IV for 5 to 14 days; ACV 400 to 800mg PO qid from wk 2 to 3mo	30	12	NR	3	0
		ALG	IVIG 500 mg/kg wks 1, 2 and 4; 250 mg/kg wks 6 and 8; ACV 400 to 800mg PO qid from wk 2 to 3mo (HC)	42		NR	14	2

a D+/R– patients also received CMVIg (every other week of treatment for 16 wk).

b 16% of patients received either OKT-3 or ATG.

c 64% of controls received IV GCV 5 mg/kg daily during anti-rejection therapy.

d Only cadaveric transplant recipients.

ACV = aciclovir; **ALG** = antilymphocyte globulin; **ATG** = antithymocyte globulin; **bid** = twice daily; **con** = consecutive pts; **CMVIg** = cytomegalovirus hyperimmune globulin; **HC** = historical controls; **Ind** = induction treatment; **IV** = intravenous; **IVIG** = intravenous immune globulin; **NR** = not reported; **OKT-3** = muromonab-CD3; **PO** = oral; **pts** = patients; **qid** = 4 times daily; **R** = recipient; **r** = randomised; **ret** = retrospective analysis; **tid** = 3 times daily; * $p < 0.05$, ** $p < 0.0001$ *vs* aciclovir.

ceived either oral ganciclovir 1000mg daily (n = 20) or oral aciclovir 400mg 3 times daily (n = 21) for 3 to 4 months in response to positive viraemia, following initial treatment with intravenous ganciclovir (5 mg/kg/day during ALA therapy). Six months after completion of ALA therapy, 5% of patients in both treatment groups, all of whom had received antirejection therapy, developed tissue-invasive CMV disease.[45]

4.2.3 Recurrence of Cytomegalovirus (CMV)

The effect of ganciclovir on episodes of CMV reactivation has been investigated in 2 studies measuring rates of recurrence in patients who had been previously treated with ganciclovir for CMV disease or CMV syndrome.[46,47]

The first[46] investigated rates of recurrence in renal and liver transplant patients (n = 19 and 18, respectively) initially treated with intravenous ganciclovir prophylaxis (5 mg/kg twice daily for 2 to 3 weeks) followed by oral ganciclovir (2000mg daily) for 2 to 3 months. CMV subsequently recurred in 27% of patients, with 2 patients developing ganciclovir-resistant CMV disease. A greater number of D+/R– patients experienced recurrence (38.1%) compared with other serologies (12.5%); however, again this did not achieve statistical significance.[46]

In the second,[47] kidney (or kidney and pancreas) transplant patients who experienced reactivation of CMV more than 30 days after ganciclovir treatment [intravenously for 14 days followed by 10 weeks treatment with oral aciclovir (n = 103)] were compared with those who did not (n = 229). Risk factors significantly associated with a recurrent episode were: having diabetes mellitus (p = 0.04), receiving a simultaneous kidney-pancreas transplant (p = 0.004), use of acute rejection treatment (p = 0.001) and receiving a cadaver organ (p = 0.001). Serological status did not appear to be a significant determinant of subsequent CMV recurrence; however, 51% of patients experiencing a recurrent episode were D+/R– compared with 8% of D–/R– patients.[47]

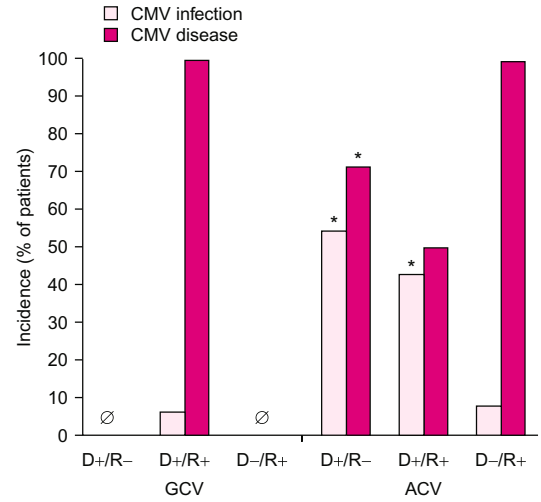

Fig. 1. Comparative efficacy of prolonged cytomegalovirus (CMV) prophylaxis with oral ganciclovir (GCV) or oral aciclovir (ACV) in kidney transplant recipients of different serologies.[38] Patients in a randomised nonblind study received oral GCV 1000mg 3 times daily for 3 months (n = 40) or oral ACV 800mg 4 times daily for 3 months (n = 39) [dosages for both drugs adjusted according to renal function]. Assessment was made at 6 months. Incidence of CMV disease is the percentage of patients with CMV infection who subsequently developed CMV disease. ø indicates no events reported; **D** = donor; **R** = recipient; * $p < 0.01$ *vs* GCV.

4.3 Lung Transplantation

The incidence of CMV disease is particularly high in lung transplant patients, with CMV pneumonia occurring in more than 75% of D+ and/or R+ patients.[48]

Studies available at the time of the last review suggested that short term ganciclovir prophylaxis (up to 6 weeks) was ineffective in preventing CMV infection.[3] Additionally, the value of long term treatment was unclear.[49] However, preliminary results[3] appeared to suggest that ganciclovir in combination with cytomegalovirus hyperimmune globulin (CMVIg) may be of therapeutic use in the prevention of CMV infection in lung transplant patients. One of these trials has since been published in full and confirmed initial findings.[50]

More recent trials have targeted treatment in 'higher risk' patients, and have generally focused on comparisons of long term intravenous with long term oral ganciclovir therapy. Some of the studies of ganciclovir in lung transplant patients have been reported in full,[51-53] although others are available only in abstract form.[54-56] The majority have targeted treatment in those patients at high or intermediate risk for development of CMV. All have employed small patient numbers.

4.3.1 Prophylactic Treatment

Table IV provides an overview of studies which have investigated the efficacy of ganciclovir as targeted prophylaxis for CMV in lung transplant patients.

A preliminary retrospective study comparing long with short term sequential ganciclovir prophylaxis in consecutive groups of patients who received no ALA induction therapy showed no benefit of long term sequential ganciclovir therapy on rates of CMV infection, CMV disease, or 12-month survival. Although the occurrence of CMV infection was higher in those on short term therapy (56 *vs* 11%), this difference was nonsignificant, probably because of small patient numbers.[54] Long term sequential intravenous/oral and intravenous ganciclovir regimens were both of significant benefit in reducing the incidence of CMV disease compared with historical controls receiving no antiviral prophylaxis in a small study.[52] Prolonged use of oral ganciclovir monotherapy has shown similar efficacy to intravenous ganciclovir with[55] or without[56] aciclovir in 2 retrospective trials reported in abstract form only (table IV).[55,56]

Patients administered short term targeted prophylaxis with intravenous ganciclovir in a retrospective analysis tended to have lower rates of both CMV infection and disease than patients who received no antiviral therapy, although this difference was nonsignificant.[51]

Patients receiving once daily intravenous ganciclovir prophylaxis (n = 35) in a randomised comparative study had a lower 12-month mortality rate (14%) than those receiving 3 times-weekly prophylaxis (n = 37; 35%; $p < 0.05$), although this was not attributable to a reduction in CMV-related disease. Rates of CMV infection and disease were similar.[53]

4.3.2 Pre-Emptive Treatment

The efficacy of pre-emptive treatment with ganciclovir in lung transplant patients had not been documented at the time of the previous review. Subsequently, similar rates of CMV disease have been observed in patients administered either pre-emptive or prophylactic therapy with intravenous ganciclovir. In a retrospective comparative study, 6 of 19 lung transplant recipients (D–/R+ and D+/R–) were treated pre-emptively with ganciclovir (5 mg/kg intravenously twice daily for 5 days, then 5 mg/kg/day to 4 weeks) and results for all 19 patients were compared with those for historical controls (n = 21; D–/R+ and D+/R–) who had received ganciclovir prophylaxis (5 mg/kg intravenously twice daily for 2 weeks, followed by 5 mg/kg/day 5 days per week for 4 weeks). CMV disease occurred in 38% of patients treated prophylactically; none of the 6 patients given pre-emptive ganciclovir later developed CMV disease.[48]

4.3.3 Deferred Treatment

Results of 1 nonblind comparative study using deferred ganciclovir treatment have been reported in abstract form only.[57] Patients in a deferred treatment group (n = 53) received a 2-week course of ganciclovir (dosage and regimen not stated) 3 to 4 weeks post-transplant, while controls (n = 33) received no antiviral prophylaxis (or a short, early course of ganciclovir). All patients received oral aciclovir (800mg 3 times daily) for 6 months post-transplant when not taking ganciclovir. In addition, D+/R– patients were also administered CMVIg (100 mg/kg at weeks 2, 4, 6 and 8). Consequently, 9% of patients receiving delayed ganciclovir prophylaxis developed CMV disease compared with 33% of controls ($p = 0.013$). Moreover, no seropositive patients who received deferred treatment (n = 38) subsequently developed CMV disease, in comparison with 36% of 25 seropositive controls ($p < 0.0001$).[57]

Table IV. Efficacy of ganciclovir (GCV) as targeted prophylaxis for cytomegalovirus (CMV) infection in lung transplant recipients: data from nonblind comparative studies. Some patients received antilymphocyte antibody (ALA) therapy

Reference (design)	CMV serology	ALA therapy	Antiviral treament regimen	No. of pts	Time of main assessment (mo)	Results (% of pts) [at main assessment unless otherwise stated]		
						CMV infection	CMV disease	mortality
IV GCV *vs* no antiviral prophylaxis								
Wreghitt et al.[51] (nb, ret)	D+/R+ D–/R+	ATG	GCV 5 mg/kg IV bid for 28 days post-transplant	27	1	59	33	
			No antiviral prophylaxis	17		82	53	
Long term IV *vs* oral GCV								
Speich et al.[a][52] (nb)	D+/R– D–/R+ D+/R+	ALG [Ind]	GCV 5 mg/kg IV bid days 7 to 21 post-transplant; GCV 5 mg/kg/day IV to day 90	5	NR		0*	
	D+/R– D–/R+ D+/R+		GCV 5 mg/kg IV bid days 7 to 21 post-transplant; GCV 1000mg PO tid to day 90	9			11*	
	D+/R+ D+/R–		No antiviral prophylaxis	8 HC			75	
Chan et al. [55] [abs] (nb, ret)	D+ and/or R+	NR	GCV 6 mg/kg IV qid for 30 days followed by ACV (800mg tid) for 11mo	34	NR	26	21	[27 at 2y]
			GCV 1000mg PO tid from day 7 post-transplant to day 126	17		NR	13	[30 at 2y]
de Pablo et al.[56] [abs] (nb, ret)	NR[b]	NR	GCV 5 mg/kg IV bid for 3wk; GCV 5 mg/kg/day for 3mo	10		20		
			GCV 5 mg/kg IV bid for 3wk; GCV 1000mg PO tid for 3mo	15		0		
Short *vs* long term GCV								
Asmi et al. [54] [abs] (nb, ret, con)	D+ and/or R+	None	GCV 5 mg/kg IV bid for 15 days; then GCV 1000mg PO tid for 15 days	16	NR	56	12.5	25 [at 12 mo]
			GCV 5 mg/kg IV bid for 30 days; then GCV 1000mg PO tid for 169 days	9		11	44	30 [at 12 mo]
Daily *vs* 3-times-weekly prolonged GCV								
Hertz et al.[53][c] (r)	D+/R– D–/R+ D+/R+	None	GCV 5 mg/kg IV bid for 2wk from day 8 then 5 mg/kg/day to day 90	35	3	3 [80 at 28mo]	[51 at 28mo]	14*[d]
			GCV 5 mg/kg IV bid for 2wk from day 8 then 5 mg/kg for 3 days/wk to day 90	37		3 [51 at 28mo]	[30 at 28mo]	35

a All D+/R– patients were given intravenously administered CMVIg.

b Only patients who had survived > 3mo were included.

c Included 5 patients receiving a simulataneous heart and lung transplant.

d Up to 36 months after transplantation.

abs = abstract; **ACV** = aciclovir; **bid** = twice daily; **CMVIg** = cytomegalovirus hyperimmune globulin; **con** = groups were treated consecutively; **D** = donor; **HC** = historical controls; **Ind** = induction treatment; **IV** = intravenous; **NR** = not reported; **PO** = orally administered; **pts** = patients; **qid** = 4 times daily; **R** = recipient; **ret** = retrospective analysis; **tid** = 3 times daily; * $p < 0.05$ *vs* comparator.

Table V. Efficacy of oral ganciclovir (GCV) as prophylaxis for cytomegalovirus (CMV) infection in liver transplant recipients: data from comparative studies

Reference (design)	CMV serology	Treatment regimen	No. of pts	Time of main assessment (mo)	Results (% of pts) [at main assessment unless stated otherwise]		
					CMV infection	CMV disease	mortality
Oral GCV *vs* placebo (PL)							
Gane et al.[62] (r, db, pc)	D+/R– D–/R+ or D+/R+	GCV 1000mg PO tid started within 10 (med 7) days of transplantation to day 98	150	6	25*	5*	[7 at 12mo]
		PL	154		52	19	[10 at 12mo]
Oral GCV *vs* ACV							
Firpi et al. [65] [abs] (ret)	D+/R– D–/R+ or D+/R+	GCV 1000mg PO tid for 3mo	132	6	NR	3.0**	NR
		ACV 800mg PO bid for 3mo	141		NR	18.4	NR
Prophylaxis *vs* pre-emptive treatment							
de Vera et al.[64] [abs] (ret)	D+/R–	GCV 1000mg PO tid 12wk or IV GCV + CMVIg[a]	19	3	NR	26	[10 at 12mo]
		GCV 5mg/kg IV bid for 14 days[b]	25		NR	28	[16 at 12 mo]
Short term oral GCV *vs* long term GCV							
Bajjoka et al. [66] [abs] (r, nb)	NR	GCV 5mg/kg IV bid for 14 days; ACV 800mg PO qid for 10wk	17	6	29	24	NR
		GCV 1000mg PO tid for 14 days; ACV 800mg PO qid for 10wk	17		24	18	NR

a Doses NR.

b In response to positive antigenaemia.

abs = abstract; **ACV** = aciclovir; **bid** = twice daily; **CMVIg** = cytomegalovirus hyperimmune globulin; **D** = donor; **db** = double-blind; **IV** = intravenous; **med** = median; **nb** = nonblind; **NR** = not reported; **pc** = placebo-controlled; **PO** = orally administered; **pts** = patients; **qid** = 4 times daily; **R** = recipient; **r** = randomised; **ret** = retrospective analysis; **tid** = 3 times daily; * $p < 0.05$, ** $p < 0.001$ *vs* comparator.

4.4 Liver Transplantation

Previous studies compared prophylactic regimens of intravenous ganciclovir with various antiviral regimens; greater efficacy was shown in patients receiving ganciclovir in combination with aciclovir than in those receiving aciclovir alone.[58-60] However, intravenous ganciclovir in combination with aciclovir was significantly less effective than intravenous ganciclovir alone at preventing CMV disease in paediatric patients.[61]

Gane et al.,[62] in their seminal double-blind, placebo-controlled study (table V), established the efficacy of prolonged administration of oral ganciclovir in decreasing CMV infection and disease among liver transplant recipients at risk for primary CMV infection. Only 1 placebo-controlled study (in abstract form) has been reported since, which has investigated the efficacy of oral ganciclovir as pre-emptive treatment in D+ and/or R+ liver allograft recipients (see section 4.4.2).[63] However, experience with this treatment has increased and has been documented in recent analyses. The majority of studies have used oral ganciclovir as either prophylaxis or pre-emptive

treatment, but comparative trials involving prophylaxis have so far not been published in full.[64-66]

4.4.1 Prophylactic Treatment

The efficacy of prolonged oral ganciclovir against CMV infection and disease is well established.[62] Recent studies have compared this regimen with other antiviral regimens and are summarised in table V. However, these reports have only been published in abstract form.

A retrospective analysis comparing the efficacy of 3-months of prophylaxis with oral ganciclovir 3000 mg/day (n = 132) or oral aciclovir 1600 mg/day (n = 141) has been reported in an abstract (table V).[65] In addition to significantly decreased rates of CMV disease in those treated with ganciclovir than in those receiving aciclovir (3.0 *vs* 18.4%, $p < 0.001$), ganciclovir was also significantly more efficacious in both D+/R+ and D–/R+ patients (3 *vs* 17% and 4 *vs* 16%, respectively; both $p < 0.05$), but not in the small number of D+/R– patients (2 *vs* 26%, NS).[65]

Broadly similar rates of CMV infection and disease were observed in patients randomised to receive treatment with 2 weeks of either intravenous or oral ganciclovir treatment followed by 10 weeks treatment with aciclovir (table V).[66] Additionally, the incidence of CMV disease was similar in a retrospective study of D+/R– patients who received prophylaxis with oral ganciclovir for 3 months (26%) or intravenous ganciclovir plus CMVIg (doses not specified), or patients treated pre-emptively with intravenous ganciclovir (28%).[64]

4.4.2 Pre-Emptive Treatment

Since the previous review,[3] which indicated that ganciclovir may be used successfully as pre-emptive treatment in liver transplant recipients, experience in this field in prospective, randomised clinical trials has increased.

A randomised, double-blind, placebo-controlled study of pre-emptive oral ganciclovir therapy (reported in an abstract) found that among patients treated with oral ganciclovir (3000mg daily for 8 weeks), CMV infection or CMV disease subsequently developed in 1 (2.8%) of 35 ganciclovir recipients and 6 of 33 placebo recipients (18%; $p = 0.0285$) [fig. 2].[63] Moreover, oral ganciclovir was also effective in 19 high risk patients: 1 (11%) of 9 D+/R– ganciclovir recipients later developed CMV infection compared with 5 (50%) of 10 D+/R– placebo recipients ($p = 0.0243$).[63]

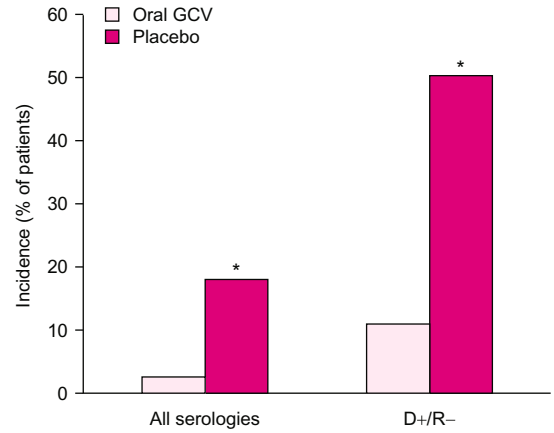

Fig. 2. Efficacy of oral ganciclovir (GCV) as cytomegalovirus (CMV) pre-emptive treatment in liver transplant recipients.[63] Patients received oral GCV 3000mg daily for 8 weeks upon detection of CMV by PCR (n = 35) or placebo (n = 33) in a double-blind study. D+/R– indicates donor seropositive/recipient seronegative (n = 9 for GCV and n = 10 for placebo). **PCR** = polymerase chain reaction; * $p < 0.05$ *vs* placebo.

No significant differences in the incidence of CMV infection, CMV disease or patient survival at 12 months were observed in a prospective, randomised nonblind comparison of 72 consecutive liver transplant patients. Patients received pre-emptive therapy with either oral ganciclovir (2000mg 3 times daily for 2 weeks followed by 1000mg 3 times daily for 4 weeks) or intravenous ganciclovir (5 mg/kg twice daily for 7 days) upon detection of positive antigenaemia. CMV disease subsequently occurred in 1 (9%) of 11 patients treated with intravenous ganciclovir. No CMV disease was observed in patients treated with oral ganciclovir (n = 11), or in those who were antigenaemia-negative (n = 50).[67]

Pre-emptive ganciclovir plus CMVIg therapy in asymptomatic CMV-seropositive liver transplant recipients was compared with no treatment in a control group (who were also CMV-seropositive) in a fully published prospectively designed non-blind trial. Consequently, 0 of 16 patients receiving pre-emptive therapy with both intravenous ganciclovir (7.5 mg/kg daily for 2 weeks) and CMVIg (100 U/kg/day on days 1, 3, 5 and 50 U/kg days 7, 9, 11 and 13) developed CMV disease compared with 2 of 15 control patients (13%) who were subsequently successfully treated.[68]

4.5 Heart Transplantation

Inconsistent results were reported in the previous review[3] from 2 placebo-controlled trials evaluating the use of intravenous ganciclovir prophylaxis in heart transplant recipients.[69,70] Prophylaxis (5 mg/kg 3 times per week) in 1 study significantly reduced rates of CMV disease only in D+/R– patients,[69] yet significantly decreased rates of CMV disease were reported in patients of all serologies who had received prophylaxis 5 mg/kg 5 times per week for 2 weeks.[70]

4.5.1 Prophylactic Treatment

Prophylaxis with ganciclovir has since been compared with no antiviral treatment in 2 studies (table VI).[51,71] Despite a trend toward improved outcomes, no significant benefit of 4 weeks' intravenous ganciclovir prophylaxis (over no antiviral treatment) was observed in high risk patients (D+ and/or R+) also receiving ATG.[51] Additionally, patients (D+ and/or R+) who received a 3-month course of oral ganciclovir (dosages not reported) following initial treatment with intravenous ganciclovir had a 3-fold increase in rates of CMV infection compared with patients (all serologies) who received no antiviral prophylaxis (p-value not reported) in this retrospective study.[71]

A retrospective analysis of a placebo-controlled trial[70] investigating the efficacy of intravenous ganciclovir 5 to 6 mg/kg/day in heart transplant recipients (for 28 days post-transplantation) demonstrated a significantly decreased incidence of transplant-associated coronary artery disease in patients who did not receive calcium antagonists and were treated with either ganciclovir (n = 28) or placebo (n = 25; 32 *vs* 62%, respectively; $p < 0.03$).[74]

Long term sequential intravenous/oral ganciclovir therapy was significantly more efficacious in preventing CMV disease than intravenous ganciclovir followed by oral aciclovir therapy in a retrospective study of consecutive heart transplant patients.[72] No differences in rates of infection were observed between transplant patients receiving sequential intravenous/oral ganciclovir, and those receiving combination CMVIg and aciclovir in a nonblind trial.[73]

4.5.2 Pre-Emptive Treatment

Little information is available regarding the use of pre-emptive therapy in heart transplant patients. One recent abstract of a small trial reported on the use of pre-emptive therapy in D+/R– patients.[75] Patients (n = 8) received 1 dose of intravenous CMVIg (2 mg/kg) and intravenous ganciclovir (5 mg/kg twice daily for 7 days) in response to positive antigenaemia. High risk historical controls (n = 6) received ganciclovir prophylaxis (5 mg/kg intravenously twice daily for 14 days); all 6 patients subsequently developed CMV disease. In contrast, although all patients pre-emptively treated developed CMV infection, significantly fewer (25%) went on to develop CMV disease ($p = 0.0047$).[75]

5. Tolerability

The tolerability of ganciclovir has been previously reviewed in *Drugs*.[3] Subsequent comparative studies have had small sample sizes or been reported in abstract form and have not been included in this update. Therefore, this section provides an overview of previous findings from controlled clinical trials.

5.1 Haematological Adverse Events

Adverse effects associated with ganciclovir therapy are generally of a haematological nature, with neutropenia, thrombocytopenia and anaemia the primary dose-limiting toxicities.[17] Neutropenia usually develops early in treatment, and is

Table VI. Efficacy of ganciclovir (GCV) as prophylaxis for cytomegalovirus (CMV) infection in heart transplant recipients: data from comparative studies

Reference (design)	CMV serology	ALA therapy	Antiviral treatment regimen	No. of pts	Time of main assessment	Results (% of pts) [at main assessment unless otherwise stated]		
						CMV infection	CMV disease	mortality
Comparison of GCV with placebo (PL) or no antiviral treatment								
Macdonald et al.[69] (r, db, pc)	D+ and/or R+	ATG	GCV 5 mg/kg IV during conditioning then 3 days/wk for 6wk	28	120 days		25 (D+/R+ or D–/R+) or 11* (D+/R–)	
			PL	28			25 (D+/R+ or D–/R+) or 71 (D+/R–)	
Merigan et al.[70] (r, db, pc)	All pts	OKT-3	GCV 5 mg/kg IV bid for 2wk from day after transplantation then 6 mg/kg od for 5 days/wk for 2wk	76	120 days	20 [19* at 60 days]	16*	9*
			PL	73		29 [56 at 60 days]	43	46
Wreghitt et al.[51] (nb)	D+/R–	ATG	GCV 5 mg/kg IV bid for 4wk	14	1mo	64	29	NR
			No antiviral prophylaxis	17		71	53	NR
Kubak et al. [71] [abs] (ret)	D+ and/or R+	NR[a]	GCV IV 2wk; GCV PO 3mo[b]	32		38[c]	NR	NR
	All pts		No antiviral prophylaxis	75		13	NR	NR
Sequential GCV regimen *vs* combination therapy								
Mullen et al.[72] (ret)	All pts[d]	NR	GCV 5 mg/kg IV bid for 14 days followed by GCV PO 1000mg tid for 90 days	62	6mo	NR	2*	[14 at 12mo]
			GCV 5 mg/kg IV bid for 14 days followed by ACV PO 800mg tid for 90 days	77		NR	18	[8 at 12mo]
Benjaminovitz et al.[73] [abs] (nb)	D+/R– D+/R+ D–/R+	NR	GCV 2.5 to 5 mg/kg IV bid for 3 days followed by GCV PO[b] for 6mo	36	NR	8	NR	0
			CMVIg IV and ACV PO[b] for 16wk post-transplant	73		18	NR	1[e]

a Patients received non-induction immunosuppression (not specified).

b Dosage NR.

c p-Value NR.

d 26 patients were removed from the analyses because they were D–/R–, or died within days of transplantation.

e Only CMV-related deaths were included.

abs = abstract; **ACV** = aciclovir; **ALA** = antilymphocyte antibody; **ATG** = antithymocyte globulin; **bid** = twice daily; **CMVIg** = cytomegalovirus hyperimmune globulin; **con** = consecutive pts; **D** = donor; **db** = double-blind; **IV** = intravenous; **mo** = months; **nb** = nonblind; **NR** = not reported; **od** = once daily; **OKT-3** = muromonab-CD3; **pc** = placebo-controlled; **PL** = placebo; **PO** = orally administered; **pts** = patients; **R** = recipient; **ret** = retrospective analysis; **tid** = 3 times daily; * $p < 0.05$ *vs* comparator.

reversible with either dosage interruption or dosage reduction. However, prolonged or irreversible neutropenia resulting in bacterial or fungal sepsis and subsequent death have been reported.[76]

Neutropenia and thrombocytopenia occurred in 6 and 5% of liver allograft recipients, respectively, who had received oral ganciclovir prophylaxis (1000mg 3 times daily) in a randomised, placebo-controlled trial versus 3 and 6% in placebo recipients. Elevated serum creatinine levels were reported in 39% of patients receiving ganciclovir versus 42% of the placebo group (16 *vs* 9.7% for levels >200 μmol/L).[62]

BMT recipients appear to be especially susceptible to the development of ganciclovir-induced neutropenia. In a randomised, placebo-controlled trial of intravenous ganciclovir prophylaxis (5 mg/kg twice daily) in patients receiving a heart transplant, neutropenia [absolute neutrophil count (ANC) ≤1000/μl] and thrombocytopenia (≤50 × 10^3 platelets/μl) occurred in 7 and 8% of patients treated with ganciclovir, respectively, and 11 and 4% of placebo recipients, respectively.[70] In contrast, thrombocytopenia and neutropenia were observed in 41 and 57% of patients, respectively, in 2 randomised, placebo-controlled trials of BMT patients who had received intravenous ganciclovir prophylaxis (5 mg/kg) versus 23 and 65% in placebo recipients.[77,78]

Continued CMV prophylaxis with intravenous ganciclovir in BMT recipients is frequently associated with neutropenia and opportunistic infections.[3] A large double-blind comparison of pre-emptive and prophylactic treatment with intravenous ganciclovir found no significant differences in the incidence of neutropenia between treatment groups (32 *vs* 25%, respectively), although prophylactically treated patients had a higher incidence of invasive fungal infections than their early-treated counterparts (16 *vs* 6% of those alive at day 100, p = 0.03).[25] Several factors have been significantly associated with neutropenia in multivariate analyses, including hyperbilirubinaemia at the start of ganciclovir therapy (p = 0.03),[30] low marrow cellularity and elevated serum creatinine levels (p = 0.0002 and p = 0.0001, respectively).[79]

No significant differences were observed between BMT patients pre-emptively treated with intravenous ganciclovir (5 mg/kg twice daily for 15 days) or foscarnet (90 mg/kg twice daily for 15 days) with respect to the incidence of leucopenia (>30% decrease in white blood cell count; 68 *vs* 45%) and thrombocytopenia (>30% reduction in platelet count from baseline; 25 *vs* 11%) in a randomised study.[29] However, Reusser et al.[28] observed significantly fewer patients with severe neutropenia who had been treated with intravenous foscarnet (60 mg/kg twice daily for 2 weeks; 4%) than intravenous ganciclovir (5 mg/kg twice daily for 2 weeks; 11%, p = 0.04).

5.2 Other Adverse Events

Renal function monitoring is recommended (section 6) for patients receiving ganciclovir, especially for those concomitantly receiving nephrotoxic drugs.[17] A high incidence of impaired renal function has been observed in transplant patients receiving intravenous ganciclovir in controlled clinical trials,[29,70,78] with elevated serum creatinine values (≥130 to <220 μmol/L) observed in 43 to 58% of patients enrolled in these trials. However, this is usually reversible when the drug is withdrawn.[80]

The incidence of impaired renal function (serum creatinine increase ≥100%, or creatinine clearance decrease ≥50% from baseline) was similar in BMT recipients treated pre-emptively with either intravenous ganciclovir 5 mg/kg twice daily for 2 weeks (5%) or foscarnet 60 mg/kg twice daily for 2 weeks (2%) in a randomised, nonblind study.[28]

Ganciclovir may also have adverse effects on the nervous system. Headache and confusion have occurred in 17 and 6% of transplant patients receiving intravenous ganciclovir during placebo-controlled trials.[76] Additionally, transient uni- or bilateral sixth nerve palsies have been reported in BMT patients receiving concomitant ganciclovir and cyclosporin.[81] Ganciclovir-induced psychosis has also been reported in 1 patient.[82]

6. Dosage and Administration

Both intravenous and oral ganciclovir are approved for use in the prevention and treatment of CMV disease in bone marrow and solid organ transplant recipients in numerous countries worldwide.

The recommended oral ganciclovir schedule for the prevention of CMV disease in allograft recipients with normal renal function is 1000mg 3 times daily with food. Intravenous ganciclovir should be reconstituted in sterile water and administered constantly over 1 hour (5 mg/kg) every 12 hours for 7 to 14 days. This should be followed by 5 mg/kg once daily, 7 days per week, or 6 mg/kg once daily, 5 times per week.[17]

Prophylaxis for 3 or 4 months was used in many clinical trials; the most commonly used regimen for the pre-emptive treatment of CMV infection in clinical trials was 5 mg/kg twice daily for 2 weeks. The duration of treatment will vary with the degree of immunosuppression. Treatment with intravenous ganciclovir has continued until day 100 to 120 post-BMT; however, this did not prevent the occurrence of some late-onset CMV disease following discontinuation of treatment. Similarly, administration beyond day 28 may be required for heart transplantation patients in order to prevent late-onset disease. The dosage should be adjusted according to tolerability.[17]

Dosage reduction is indicated for patients with renal impairment (see section 3.2), and those with neutropenia, anaemia, and/or thrombocytopenia. It is possible that drugs inhibiting renal tubular secretion or reabsorption may interfere with the renal clearance and urinary excretion of ganciclovir. Therefore, caution is advised in patients concurrently receiving cyclosporin or amphotericin B, or other nephrotoxic drugs.[17]

Ganciclovir is contraindicated in patients with an absolute neutrophil count of <500/μl, or platelet count of $<25 \times 10^3$/μl. Additionally, patients with pre-existing cytopenias or a history of cytopenic reactions to other drugs should be closely monitored.[17]

Ganciclovir has shown both teratogenic and mutagenic properties in animal models; therefore contraception for women during treatment and barrier contraception for men both during and for 90 days post-treatment is advised.[17] However, teratogenic effects were notably absent in the offspring of a female patient who became pregnant whilst receiving ganciclovir post-liver transplantation.[83]

7. Pharmacoeconomic Considerations

Episodes of CMV disease in the renal transplant patient result in increased treatment costs.[84,85] An incremental length of hospital stay of between 12[85] and 37[84] days for renal transplant patients developing CMV disease has been reported relative to controls without CMV disease, with incremental hospital costs of between $US5700 and $US12 500 (1987 values)[85] and $Can25 000 (1988 values).[84]

Management strategies aimed at the prevention of CMV are therefore of potential benefit in terms of both patient outcomes and resource savings. A number of ganciclovir regimens have been employed in an effort to reduce both CMV-related morbidity and CMV-related mortality (section 4) and this section provides an overview of currently available pharmacoeconomic information for these in comparison with other available antiviral regimens (summarised in table VII).

7.1 In Renal Transplantation

The cost effectiveness of intravenous ganciclovir prophylaxis in high risk renal transplant recipients (expressed as cost per case of CMV disease avoided) was compared with 4 other strategies in a decision-tree model (from the UK National Health Service perspective) based on outcomes from published clinical trial results (table VII).[86] Treatment algorithms for the development of CMV syndrome and tissue-invasive disease were constructed using published literature and UK physician interviews. The baseline incidence of CMV disease was assumed to be 45%.[86] Prophylaxis with either oral valaciclovir (90 days) or intrave-

Table VII. Comparative pharmacoeconomic analyses of ganciclovir (GCV) regimens in kidney, lung and liver allograft recipients. Only direct costs arising from hospital and/or outpatient contacts and medication were considered

Reference	Country of economic analysis (currency year)	Antiviral regimen [duration]	Source of primary and cost data [perspective]	Mean direct medical costs per patient	Incremental cost-effectiveness ratio [expressed as cost per case of CMV disease avoided unless otherwise stated]
Kidney transplantation					
Schnitzler et al.[87] [abs]	US (NR)	Oral GCV [90 days[a]]	Hospital costs, Medicare payments [NR]	$US40 541 at 240 days	$US13 528
		Pre-emptive oral GCV [84 days]		$US41 992 at 240 days	$US17 558
		Deferred IV GCV and oral ACV		$US35 877 at 240 days	Reference
Schnitzler et al.[88]	US (1996)	Deferred IV GCV [3wk]	RCT nonblind [providers of medical care]	$US13 020 at 1y [$US26 628 at 3y]	NR
		Pre-emptive IV GCV [3wk]		$US9247 at 1y [$US11 351* at 3y]	NR
Mauskopf et al.[86][b]	UK (1996)	Oral VAL [90 days]	Published literature, interviews with physicians [UK National Health Service]	£4748	£8111
		IV GCV [2wk]		£4310	Reference
		Pre-emptive IV GCV [3wk]		£4988	Dominated by prophylaxis
		Changed immunosuppression		£4420	Dominated by IV GCV prophylaxis
		Deferred IV GCV [3wk]		£6029	Dominated by prophylaxis
Lung transplantation					
Kelly et al.[48]	US (NR)	IV GCV [6wk]	Nonblind clinical trial [NR]	$US8666	Reference
		Pre-emptive IV GCV [4wk]		$US6097	$US2569 [cost savings]
Liver transplantation					
Das[89]	US (1995-adjusted)	IV GCV [100 days]	Published RCTs, hospital-based transplantation programme, expert opinion, [society[c]]	$US58 933	$US5334/QALM
		Oral GCV [100 days]		$US53 165	$US4867/QALM
		CMVIg [16wk]		$US59 160	$US5472/QALM
		Oral ACV [6mo]		$US55 243	$US4916/QALM
		Oral ACV [3mo]		$US53 482	$US4851/QALM
Goldsmith et al.[90] [abs]	US (1997)	IV GCV/oral ACV [NR]	Published RCTs, hospital costs [NR]	NR	$US46 808
		Oral GCV		NR	–$US18 891 [i.e. cost savings]
		Oral GCV/ACV		NR	–$US9325
		CMVIg/IV GCV		NR	Dominated by reference
		No prophylaxis		NR	Reference

a D+/R– and D+/R– patients received treatment for 180 days.

b This model only considered D+/R– patients.

c Indirect costs were not included.

abs = abstract; **ACV** = aciclovir; **CMVIg** = cytomegalovirus hyperimmune globulin; **D** = donor; **IV** = intravenous; **NR** = not reported; **QALM** = quality-adjusted life-month; **R** = recipient; **RCT** = randomised, controlled trial; **VAL** = valaciclovir; * $p < 0.001$ *vs* comparator.

nous ganciclovir (14 days) resulted in lower costs and fewer cases of CMV disease than both pre-emptive and deferred strategies. The cost per patient was between £157 and £438 (1996 values) higher with oral valaciclovir prophylaxis than with short term intravenous ganciclovir prophylaxis, although this altered depending on the assumed incidence of CMV disease at baseline.[86]

A 3-year follow-up of patients who received either pre-emptive or deferred treatment with intravenous ganciclovir noted an approximately 40% increase in average direct medical costs associated with deferred treatment during the first year post-

transplant ($US9247 *vs* $US13 020 per patient, p = 0.243; costs adjusted to 1996 dollars using Consumer Price Index), although this did not achieve statistical significance. However, costs in the deferred group were almost doubled those at 1 year (an additional $US15 277 per patient, p < 0.001) after 3 years (table VII).[88] This observed difference at 3 years was primarily due to increased hospitalisations in those who had received deferred treatment. It is important to note that this nonblind study included a relatively small number of patients (n = 36).[88]

In contrast, total per-patient costs at 240 days post-transplantation in patients who had received deferred intravenous ganciclovir therapy plus oral aciclovir, pre-emptive oral ganciclovir prophylaxis for 84 days, or oral ganciclovir prophylaxis for 90 days post-transplant in D–/R+ patients (180 days if D+/R– or D+/R+) were $US35 877, $US41 992 and $US40 541 (year not stated), respectively (table VII).[87] Incremental cost-effectiveness ratios for the 2 oral ganciclovir therapies, expressed as the cost per case of CMV-disease avoided, were $US17 558 and $US13 528.[87]

7.2 In Liver Transplantation

Oral ganciclovir administered prophylactically to liver transplant patients was the most favoured strategy in a cost-utility analysis of various chemoprophylactic regimens (table VII).[89] A Markov model was constructed, which compared 5 different treatment strategies in a hypothetical cohort of 1000 orthotopic liver transplant recipients over a 1-year period. Oral ganciclovir was associated with both lower costs and greater efficacy than CMVIG and oral aciclovir. Cost effectiveness was not improved when prophylaxis was restricted to defined high risk groups, or when the duration of prophylaxis was extended beyond 3 months.[89]

Another modelled cost-effectiveness analysis, published in abstract form only, found that oral ganciclovir treatment (with or without oral aciclovir) had lower costs and rates of CMV disease than a reference group receiving no prophylaxis (cost savings per patient –US$2267 and –US$1119, respectively; 1997 dollars). Costs associated with combination intravenous ganciclovir and oral aciclovir or CMVIg were higher than no prophylaxis.[90]

Similarly, a cost-effectiveness analysis based on results from a randomised, clinical trial comparing oral aciclovir with sequential intravenous ganciclovir/ oral aciclovir found that ganciclovir therapy dominated aciclovir monotherapy 93.5% of the time. The incremental cost savings of using ganciclovir were $US19 545 in D+/R– patients (year not given).[91]

7.3 In Lung Transplantation

The cost effectiveness of intravenous ganciclovir followed by continued intravenous or oral ganciclovir was investigated in a small number of lung transplant recipients (see table IV for study details).[52] Costs of treatment included hospital stay, drug acquisition costs and outpatient costs. There was no statistically significant cost difference between intravenous and oral prophylaxis (SwF16 802 *vs* SwF22 316, respectively; year not reported), mainly due to a longer treatment period in those administered oral ganciclovir (93 *vs* 210 days).[52]

Pre-emptive therapy with intravenous ganciclovir for 6 weeks (n = 19) in lung transplant recipients was associated with a net savings of $US2569 (year not given) per patient compared with historical controls treated prophylactically with intravenous ganciclovir. Similar morbidity and mortality was observed between the 2 treatments in this indirect comparison.[48]

8. Place of Ganciclovir in the Prevention of CMV in Transplant Recipients

CMV infection in transplant recipients is associated with an increased risk of opportunistic infections, allograft injury and higher transplantation costs; it also appears to increase the risk of acute and chronic rejection of allografts via immune-mediated vascular injury.[4]

Table VIII. Summary of the key properties of currently available antiviral and immunotherapeutic regimens for preventing cytomegalovirus (CMV) infection and disease in transplant recipients

Valaciclovir	Prevented CMV infection and disease in high risk kidney transplant recipients and reduced incidence of biopsy proven acute rejection[93]
Valganciclovir	High oral bioavailability (≈70%); plasma concentrations of GCV following oral administration similar to intravenous GCV[6] Comparative trials in transplant recipients not available but efficacy similar to IV GCV in AIDS-related CMV retinitis.[94]
Foscarnet	Similar efficacy to GCV;[95] only used in patients with GCV-resistant CMV or in whom GCV treatment has failed; marked nephrotoxicity[7]
CMVIg	Decreases incidence of CMV infection following BMT, does not seem to be effective in preventing CMV disease[6]
IVIG	No effect on incidence of CMV infection, but may reduce the risk of CMV disease[6]
Aciclovir	Prophylaxis reduces the incidence of CMV disease and mortality in BMT patients[96]

BMT = bone marrow transplantation; **GCV** = ganciclovir; **CMVIg** = CMV hyperimmune globulin; **IVIG** = intravenous immune globulin.

A range of treatment strategies for CMV have evolved, including administration of antiviral drugs, the identification of risk factors, early diagnosis and pre-emptive treatment of active infection and immunotherapy. None of these strategies alone has been entirely successful in the management of patients at risk for CMV infection and disease. Consequently, recommendations for treatment have not been clearly established,[21] although clinical guidelines for the treatment of CMV disease in renal allograft patients were published by Jassal et al. in 1998.[92]

Nevertheless, intravenous ganciclovir has remained the cornerstone of treatment for the prevention and treatment of CMV infection and disease in transplant patients since it became available for use in the late 1980s. Ganciclovir as an oral formulation was later approved for use in transplant recipients. The key properties of other antiviral agents are presented in table VIII.

While the efficacy of intravenous ganciclovir prophylaxis in transplant patients was well established at the time of the previous review,[3] the relative efficacy of oral ganciclovir and pre-emptive therapy was still unclear. Additional unresolved issues were the role of prolonged administration of ganciclovir on the development of ganciclovir-resistant CMV strains, and the cost effectiveness of both oral and intravenous ganciclovir therapies.

The majority of studies published since the last review have been retrospective analyses comparing CMV morbidity or mortality outcomes after a change in regimens in a transplant programme. In addition, many of the studies in solid organ transplantation have included only small patient numbers, reducing the statistical power of these studies. Therefore, the inherent weaknesses in the design of studies which have addressed the role of ganciclovir in CMV since the previous review should be borne in mind when evaluating the results.

The success of any approach aimed at the prevention and treatment of CMV is likely to depend upon the type of transplantation, the level of risk for individual transplant recipients, and the immunosuppressive and antiviral regimens employed. The situation is different for BMT recipients compared with solid organ transplant recipients and these patients are dealt with separately in the following sections.

8.1 In Bone Marrow Transplantation

Both prophylactic and pre-emptive strategies are widely used for the prevention of CMV infection and disease in BMT patients.[97] A survey of BMT programmes in the US found that approximately 55% employ pre-emptive therapy and ≈20% use prophylactic therapy.[98] However, the superiority of one treatment over the other in preventing CMV infection has not been established. Recent studies comparing the relative efficacies of prophylactic and pre-emptive ganciclovir therapies have shown similar rates of CMV infection, CMV disease and mortality between the 2 treat-

ments (section 4.1.1). A commensurate reduction in patient mortality following ganciclovir prophylaxis was not observed in some studies[77,99] because of ganciclovir-induced neutropenia, which appeared to counterbalance the beneficial effects of treatment. Subsequent comparative studies have similarly reported no improvement on survival outcomes (section 4.1.1). Sensitive diagnostic tests for CMV (such as the pp65 antigenaemia or PCR-DNA assays), reviewed in detail elsewhere,[80] now allow the early identification of CMV infection at an earlier stage than previously, when systemic viral load may still be low.[100,101] It is hoped that the use of these tests may reduce CMV-related mortality during risk-adapted approaches.[102]

Pre-emptive strategies were initiated in an attempt to reduce the adverse effects associated with ganciclovir, although evidence suggests that there is little difference in the adverse effect profiles of the 2 treatments.[3] However, universal prophylaxis with ganciclovir undoubtably results in overtreatment and unnecessarily exposes some patients to the drug. Adverse effects associated with intravenous ganciclovir remain an important consideration in the treatment of BMT patients. Attempts to decrease the frequency of ganciclovir administration to alleviate treatment-related adverse effects have resulted in loss of efficacy (section 4.1.1).

Early studies suggested a beneficial effect of aciclovir compared with placebo, but prospective comparisons of ganciclovir and aciclovir are still not available and therefore the relative efficacy of these drugs in preventing CMV in BMT recipients cannot be conclusively determined. The addition of aciclovir to ganciclovir prophylactic therapy has shown no demonstrable benefit over pre-emptive ganciclovir monotherapy (section 4.1.1).[27] However, recently intravenous pre-emptive foscarnet has proved equally as efficacious as pre-emptive treatment with intravenous ganciclovir (table II), with potentially less myelosuppression.[28,29]

Late-onset CMV disease (after 100 days) continues to be a major cause of morbidity and mortality after BMT.[24,101] Patients administered prolonged treatment (>100 days) with either prophylactic or pre-emptive ganciclovir are not able to fully reconstitute the immune response to CMV and are therefore at increased risk for the development of both late-onset CMV and bacterial and fungal infections after discontinuation of treatment.[6,24,25,79,101,103]

Other agents, such as oral ganciclovir, valaciclovir and valganciclovir, which are as yet untested in this population, may potentially offer better tolerability. In addition, oral agents offer ease of administration and may enable immunisation while still preventing CMV disease. Prophylaxis will result in increased drug acquisition costs and may incur extra treatment costs for secondary infections; however pre-emptive therapy requires costly regular CMV monitoring from the time of transplantation. These pharmacoeconomic issues in BMT patients remain to be elucidated.

8.2 In Solid Organ Transplantation

Prophylactic treatment with ganciclovir overall is associated with a significant reduction in risk of both CMV infection and CMV disease compared with either placebo or no treatment in prospective, controlled studies, but similar reductions in graft loss, acute rejection and mortality have not been seen.[4] Clinical practice guidelines for renal allograft patients recommend prophylaxis (antiviral regimen not specified) for patients at risk for primary CMV infection; ganciclovir prophylaxis is advised for all patients (except D–/R– patients) treated with ALA therapy.[92]

Aciclovir is commonly used as prophylaxis in the treatment of solid organ transplant recipients, although its efficacy has not been consistently demonstrated.[3] Initial positive studies in high risk renal patients led to its common use in this patient group; however, aciclovir is largely ineffective in preventing CMV infection and disease following liver, heart or lung transplantation.[3] Since then, the greater efficacy of long term oral ganciclovir over oral aciclovir as prophylaxis in predominantly D+ and/or R+ renal allograft recipients in preventing CMV infection has been shown in kidney transplantation (section 4.2.1) and CMV disease in se-

ropositive liver allograft recipients (section 4.4.1) and heart transplant recipients (section 4.5.1). Rates of CMV disease tended to be higher in seropositive kidney transplant recipients treated with oral aciclovir than in those receiving oral ganciclovir, although this difference did not reach statistical significance.[38]

Recently, however, the oral prodrugs valaciclovir and valganciclovir have shown efficacy in this indication. Oral valaciclovir reduced the incidence of CMV disease versus placebo in both seropositive and seronegative patients in a randomised, double-blind, placebo-controlled study.[104] A single, nonblind comparative trial in patients with AIDS-related CMV retinitis has shown similar efficacy for oral valganciclovir and intravenous ganciclovir and trials investigating the therapeutic use of oral valganciclovir in transplant patients are ongoing.[94]

Oral ganciclovir has generally proved effective as prophylaxis in high risk liver transplant recipients and those receiving ALA therapy.[3] Long term oral ganciclovir regimens have shown greater efficacy against CMV infection than no antiviral prophylaxis in D+ and/or R+ kidney transplant patients receiving ALA (section 4.2.1), and lung transplant patients receiving antilymphocyte globulin (section 4.3.1) but not in heart transplantation (section 4.5.1). Additionally, relatively low dosages of oral ganciclovir may be effective in kidney allograft recipients not receiving ALA therapy (section 4.2.1); higher dosages may be indicated for those receiving ALA, although this will require further investigation.

Whether oral ganciclovir may have value in the pre-emptive treatment of asymptomatic CMV infection is still unclear. Pre-emptive therapy was largely untested in solid organ transplantation at the time of the previous review. Since then, the majority of studies employing this strategy have involved liver allograft patients (section 4.4.2). Generally, pre-emptive therapy with either oral or intravenous ganciclovir has demonstrated similar efficacy to prophylactic therapy, although this remains to be confirmed in well-designed trials.

Administration of short courses of intravenous ganciclovir have not been associated with viral resistance;[105] however, viral resistance is a problem with prolonged administration of antiviral therapies in patients with HIV infection.[12] Moreover, ganciclovir-resistant CMV has been identified as an important cause of late morbidity among D+/R– transplant recipients who have had prolonged exposure to ganciclovir and have received intense immunosuppression.[11,12] It may be that viral loads in these high risk patients are only partially suppressed by ganciclovir and that this, in combination with lower plasma concentrations achieved with oral ganciclovir, may provide the conditions under which ganciclovir resistance can emerge. Research into strategies to reduce this complication, especially among D+/R– patients, is warranted.

However, while strategies which limit exposure to the patient, such as short term pre-emptive treatments, may be desirable in terms of preventing viral resistance, available pharmacoeconomic analyses (section 7) indicate that ganciclovir or valaciclovir prophylaxis is more cost effective than other currently available therapies for the prevention of CMV infection and disease (such as adjusted immunosuppression, aciclovir and CMVIg and combinations of these with ganciclovir). Therefore, determination of optimal treatment in the individual patient will need to balance efficacy and tolerability against potential pharmacoeconomic benefits. Further pharmacoeconomic comparisons of intravenous and oral ganciclovir would be useful.

8.3 Conclusions

It is unlikely that a single strategy will be able to be applied to all transplant recipients for the prevention of CMV disease. However, the best strategy for each patient will probably depend on the risk of CMV disease following transplantation and the adverse effects associated with treatment. A risk-adapted approach to treatment of CMV may prove most efficacious. Prophylactic treatment appears the optimal strategy to implement in patients at high risk for development of CMV infection or

disease (such as those receiving ALA therapy); oral formulations may be best employed where lower toxicity is required. Pre-emptive treatment appears most efficacious in patients identified as lower risk or, in the case of BMT recipients, where lower toxicity may be desirable. Ganciclovir remains an important therapeutic option for the prevention and treatment of CMV disease in transplant recipients.

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