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Ganciclovir

An Update of its Therapeutic Use in Cytomegalovirus Infection

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Synopsis

The antiviral nucleoside analogue ganciclovir has demonstrated in vitro *activity against human cytomegalovirus and effectively treats infection caused by this organism in various immunocompromised patient groups. The drug prolongs time to progression in patients with acquired immune deficiency syndrome (AIDS)-related cytomegalovirus retinitis although life-long maintenance therapy is required. Direct comparisons between ganciclovir and foscarnet in this indication are few; nevertheless, the 2 drugs appear to have equal therapeutic efficacy in treating cytomegalovirus retinitis although results from 1 study in this indication suggest that foscarnet has an advantage in terms of patient survival. AIDS-related gastrointestinal and, to a lesser extent, pulmonary cytomegalovirus infection also respond to treatment with ganciclovir; maintenance therapy does not appear to be required in these latter 2 indications. Ganciclovir is also useful against cytomegalovirus infection in organ transplant recipients. The drug is most effective when given prophylactically or as early treatment for asymptomatic infection in bone marrow transplant recipients; treatment of established infection is less effective in this patient group. However, established infection in solid organ transplant recipients appears to respond to treatment with ganciclovir.*

The most common adverse event during ganciclovir therapy is haematological toxicity but this appears to be readily reversible on discontinuation of the drug. In addition, coadministration of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) has been shown to prevent ganciclovir-associated neutropenia.

Thus, ganciclovir is a valuable treatment for cytomegalovirus infection in patients with AIDS and in organ transplant recipients. Further studies comparing ganciclovir and foscarnet – ideally incorporating the use of G-CSF or GM-CSF to prevent ganciclovir-associated neutropenia and assessing survival as 1 endpoint – should further clarify the relative role of ganciclovir as treatment or prophylaxis for cytomegalovirus infection.

Antiviral Activity

Ganciclovir has demonstrated good *in vitro* activity against human cytomegalovirus and is considerably more potent than aciclovir (acyclovir) against this organism. The combination of ganciclovir and foscarnet synergistically inhibited replication of human cytomegalovirus *in vitro*. The presence of ganciclovir reduced the *in vitro* activity of zidovudine against human immunodeficiency virus in 2 studies but enhanced it in another.

Ganciclovir has demonstrated *in vivo* efficacy in animal models including

disseminated and pulmonary murine cytomegalovirus infection and murine cytomegalovirus encephalitis.

Cytomegalovirus strains resistant to ganciclovir appear to have point mutations in a gene encoding a kinase that phosphorylates ganciclovir and another encoding a viral DNA polymerase. The true incidence of resistance to ganciclovir is still unclear; however, the clinical impact of resistance has been minimal to date.

Pharmacokinetic Properties

Intravenous administration of 1 to 5 mg/kg doses of ganciclovir produces linearly increasing peak plasma concentrations; no evidence of accumulation has been observed in patients with normal renal function. Intravitreal administration of ganciclovir produces high concentrations in vitreal fluid with minimal, if any, systemic absorption.

The bioavailability of orally administered ganciclovir was approximately 6% after administration of 10 mg/kg, or 1000mg doses.

Concentrations of ganciclovir in cerebrospinal fluid were lower than those reported in serum after intravenous administration. Ganciclovir has a steady-state volume of distribution of approximately 32 to 44.5 L/1.73m^2. Almost 100% of an intravenously administered dose of ganciclovir is excreted in the urine of patients with normal renal function. The drug has an elimination half-life of between 2 and 4 hours after intravenous administration of 1 to 5 mg/kg doses. Clearance decreases linearly with decreasing creatinine clearance in patients with renal dysfunction. Ganciclovir is effectively cleared by haemodialysis.

Therapeutic Use

Symptomatic cytomegalovirus infection occurs predominantly in immunocompromised patients; thus, most studies evaluating the efficacy of ganciclovir against cytomegalovirus infection have been conducted in this patient group. Many noncomparative trials suggest that intravenous ganciclovir is an effective treatment for acquired immune deficiency syndrome (AIDS)-related cytomegalovirus retinitis. Rapid progression of retinitis has been observed when ganciclovir therapy is deferred in patients whose retinitis is not an immediate threat to sight. Combination therapy with ganciclovir and either foscarnet or (to a lesser extent) cytomegalovirus immune globulin appears to be effective, especially in patients refractory to ganciclovir monotherapy.

Few direct comparisons of ganciclovir and foscarnet have been conducted. Although the 2 drugs appear to be similar in terms of efficacy against cytomegalovirus retinitis, the Studies of Ocular Complications of AIDS (SOCA) research group and AIDS clinical trials group (ACTG) trial revealed a survival advantage in foscarnet versus ganciclovir recipients in this indication.

Intravitreal injection of ganciclovir has been shown to be as effective as intravenous administration for treatment of AIDS-related cytomegalovirus retinitis and has proven useful in patients unable to tolerate systemic administration. Preliminary studies of sustained-release intraocular formulations designed to improve patient acceptability have provided favourable results as have trials evaluating the use of oral ganciclovir maintenance therapy in patients with cytomegalovirus retinitis.

Limited data suggest that ganciclovir may be an effective treatment for AIDS-related gastrointestinal cytomegalovirus infection and, to a lesser extent, AIDS-related cytomegalovirus pneumonia.

A number of studies have shown ganciclovir to be a useful treatment for

established cytomegalovirus infection in adult organ transplant recipients. Results from a small number of studies in paediatric transplant recipients are also favourable. The drug has been studied as prophylaxis, early treatment of asymptomatic infection and treatment for established symptomatic infection. Although more studies are required to confirm initial findings, it appears that bone marrow transplant recipients benefit most from prophylaxis or early treatment; results from studies evaluating the treatment of established cytomegalovirus infection in this patient group are less favourable. However, treatment of established infection is effective in solid organ transplant recipients.

Results from a single pilot study suggest that 3 months' maintenance therapy with ganciclovir after 2 weeks' induction therapy improves outcome in infants with congenital cytomegalovirus infection compared with 2 weeks' therapy alone.

Tolerability

Neutropenia and thrombocytopenia are the most common adverse events in patients receiving ganciclovir, occurring, respectively, in 38 and 20% of patients who received ganciclovir during the compassionate use programme. Haematological adverse events during ganciclovir therapy are usually reversible on withdrawal of the drug. Preliminary studies suggest that concomitant administration of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) can prevent ganciclovir-associated neutropenia and confirmatory results are awaited with interest. Less common adverse events reported during ganciclovir therapy include central nervous system symptoms, abnormal liver function values, fever and rash.

Drug Interactions

The toxicity profiles of ganciclovir and zidovudine overlap and reduction of the zidovudine dosage is sometimes required in patients receiving the 2 drugs concomitantly. Concurrent administration of ganciclovir with other drugs that inhibit replication in rapidly dividing cell populations is not recommended.

Dosage and Administration

The recommended dosage regimen for ganciclovir as treatment for patients with cytomegalovirus retinitis and normal renal function is 5 mg/kg (as a constant intravenous infusion over 1 hour) every 12 hours for 14 to 21 days. If required, maintenance doses of 5 mg/kg/day (as a constant intravenous infusion over 1 hour) 7 days/week, or 6 mg/kg/day (similarly administered) 5 days/week, can be given following the initial induction regimen. The same dosages with a shorter (7 to 14 days) induction regimen are recommended for the prevention of cytomegalovirus disease in transplant recipients. The drug should be infused over a 1-hour period. Subcutaneous or intramuscular administration is not recommended.

Dosage reductions according to creatinine clearance are recommended in patients with renal impairment.

Intravitreal ganciclovir is generally given at a dose of 200 to 400μg once or twice weekly during induction therapy, weekly maintenance doses are then given.

Extreme caution is warranted before ganciclovir is used in children, because the safety of the drug in this population has not been established.

Ganciclovir (fig. 1), a 2′-deoxyguanosine analogue with therapeutic activity against human cytomegalovirus infection, was first reviewed in *Drugs* in 1990.[1] A number of important trials evaluating the use of ganciclovir in this indication have subsequently been published and the drug has been widely used in clinical practice. This review re-examines the use of ganciclovir in human cytomegalovirus infection providing an overview of the most relevant pharmacological and clinical findings from the initial review supplemented by more recently published data. The activity of ganciclovir against Herpesviridae other than human cytomegalovirus, and against other DNA viruses, is not addressed.

1. Activity Against Human Cytomegalovirus

1.1 *In Vitro* Activity

Results from many studies[2-14] have confirmed the good *in vitro* activity of ganciclovir against human cytomegalovirus and have demonstrated its superiority over aciclovir (acyclovir) in this regard (table I).

Liposomal encapsulation has been shown to enhance the activity of ganciclovir against human cytomegalovirus cultured in human embryo lung cells *in vitro*. The drug concentration producing 50% inhibition of viral replication (IC_{50}) of non-encapsulated and encapsulated drug, measured using plaque reduction assays, were 316 and 96 mg/L, respectively. The relatively high values obtained are the result of a relatively short exposure time (24 hours *vs* 10 to 12 days in other studies).[15]

Combination antiviral therapy has the potential to enhance therapeutic efficacy while decreasing adverse effects relative to monotherapy and may also retard the development of drug resistance.[16] A number of new studies evaluating potential *in vitro* synergy and antagonism between ganciclovir and other antiviral drugs have been published since the previous review,[1] which noted a lack of studies in this area.

Ganciclovir and foscarnet synergistically inhibited replication of cytomegalovirus cultured in MRC-5 cells *in vitro*. Mean IC_{50} values for ganciclovir and foscarnet alone were 2.25 and 33.25 mg/L, respectively. Ganciclovir and foscarnet in combination reduced IC_{50} values in a concentration-dependent manner.[17] Snoeck et al.[16] found that ganciclovir combined with the investigational antiviral compounds (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine (HPMPA) and (*S*) - 9 - (3 - hydroxy - 2 - phosphonylmethoxypropyl)-cytosine (GS 504) [HPMPC] synergistically inhibited growth of cytomegalovirus in human embryo lung cells *in vitro*. A further investigational compound, A1110, also potentiated the *in vitro* activity of ganciclovir against cytomegalovirus.[18] MS 109, an investigational human anticytomegalovirus monoclonal antibody, had an additive effect on the *in vitro* activity of ganciclovir against cytomegalovirus in human fibroblasts.[19]

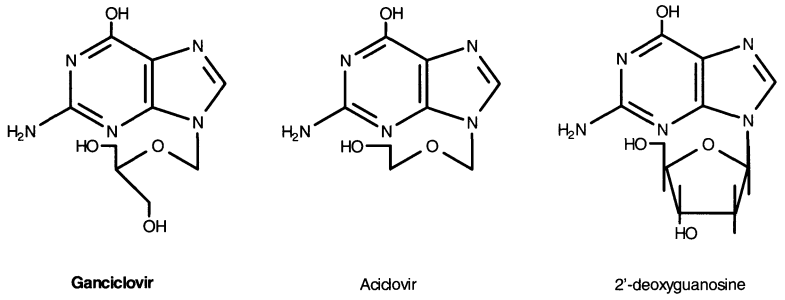

Fig. 1. Chemical structure of the acyclic nucleosides ganciclovir and aciclovir, and their purine nucleoside analogue 2′-deoxyguanosine.[1]

Table I. Summary of the *in vitro* activity of ganciclovir and other agents against human cytomegalovirus measured by plaque reduction assay (updated from Faulds & Heel[1])

Reference	Viral strain	Cell culture	Concentration achieving 50% inhibition (μmol/L)[a]		
			GCV	PFA	ACV
Andrei et al.[2]	AD169	MRC-5	1.92	23.2	120
		HEL	2.8	63.2	64
	Clinical isolates (n = 17)	MRC-5	1.92	61.6	51.6
		HEL	2.32	81.6	76.4
Biron et al.[4]	AD169	HFF	1		190
Cole & Balfour[5]	AD169	HFF	3.1		60.5
Duke et al.[6]	AD169	MRC-5	4.5		
	Davis		4.9		
Konno et al.[7]	Clinical isolates (n = 52)	NR	0.73		
Rush & Mills[8]	AD169	HFF	0.43		100
Shigeta et al.[9]	AD169	MRC-5	3.1		25
	NS-15		3.1		25
	NS-84		3.1		25
Smee et al.[10]	AD169	MRC-5	7		95
Snoeck et al.[11]	AD169	HEL	2.73		
	Davis		1.95		
Taylor et al.[13]	Kerr	HEF	0.6		
Tolman et al.[14]	AD169	MRC-5	3		10

a Results reported in mg/L were converted to μmol/L. Results were reported as the drug concentration inhibiting viral plaques, DNA synthesis, antigen expression or virus-induced cytopathogenicity by 50%.

Abbreviations: ACV = aciclovir; GCV = ganciclovir; HEL = human embryo lung fibroblasts; HEF = human embryo fibroblasts; HFF = human foreskin fibroblasts; MRC-5 = human embryo lung cells; NR = not reported; PFA = foscarnet.

Feng et al.[20] reported reduced *in vitro* activity of ganciclovir against cytomegalovirus cultured in human embryo lung cells in the presence of zidovudine. Medina et al.[21] and Cox et al.[22] reported that ganciclovir reduced the *in vitro* activity of zidovudine against human immunodeficiency virus. A further study suggests that the presence of ganciclovir reduces intracellular phosphorylation of zidovudine in a concentration-dependent manner.[23] In contrast, comprehensive analyses by Freitas et al.[24] using 3-dimensional linear regression analysis found zidovudine to have an additive effect on the *in vitro* activity of ganciclovir against human cytomegalovirus.

1.2 *In Vivo* Activity

An animal model of human cytomegalovirus infection has recently been developed, with successful inoculation of severe combined immunodeficient mice implanted with human fetal tissue reported by Mocarski et al.[25] However, the effects of ganciclovir in this model have not yet been described. Ganciclovir appeared to be more effective than aciclovir as treatment for pulmonary murine cytomegalovirus infection in mice and, in combination with cytomegalovirus antiserum, was more effective than ganciclovir monotherapy in disseminated murine cytomegalovirus infection and murine cytomegalovirus encephalitis.[1] To determine whether antiviral treatment is able to eliminate cytomegalovirus-associated immunosuppression, Banister and Pomeroy[26] administered ganciclovir to mice with previously dormant *Toxoplasma gondii* infection reactivated by murine cytomegalovirus infection. Ganciclovir therapy started 1 day before inoculation with cytomegalovirus reduced the severity of cytomegalovirus-induced *T. gondii* infection whereas initiation of

ganciclovir therapy 2 days after inoculation did not.

1.3 Mechanism of Action

Ganciclovir is phosphorylated within virus-infected cells to form an active nucleotide.[27-29] Levels of ganciclovir 5′-mono- and diphosphate in infected cells are lower than ganciclovir triphosphate levels, suggesting that the initial phosphorylation of ganciclovir is the rate limiting step.[3,30]

Early research suggested that an induced host-encoded deoxyguanosine kinase facilitated the production of ganciclovir monophosphate in cytomegalovirus-infected cells.[3,31,32] However, more recent evidence suggests that the UL97 open reading frame of human cytomegalovirus encodes a protein capable of regulating the phosphorylation of ganciclovir.[33,34]

After its formation, ganciclovir 5′-monophosphate is further phosphorylated by cellular kinases to the di- and triphosphate forms. Induction of these cellular kinases has been demonstrated in cells infected with human cytomegalovirus.[32,35]

The activity of ganciclovir against human cytomegalovirus results primarily from inhibition of viral DNA synthesis by ganciclovir triphosphate.[1,36] Ganciclovir triphosphate competitively inhibits incorporation of dGTP into DNA and is also directly incorporated into viral DNA, impeding and prematurely terminating its elongation.[37]

1.4 Mechanisms of Viral Resistance to Ganciclovir

Certain patients with cytomegalovirus infection unresponsive, or progressively less responsive, to long term ganciclovir therapy have been shown to harbour strains with reduced, or progressively diminishing, *in vitro* sensitivity to ganciclovir.[38,39] In some cases these ganciclovir-resistant strains remained sensitive to foscarnet, and recently a foscarnet-resistant, ganciclovir-sensitive cytomegalovirus isolate was reported suggesting different mechanisms of resistance to the 2 drugs.[40]

Further investigation has revealed that phosphorylation of ganciclovir did not occur in cells infected with these less sensitive strains.[41] Point mutations in 2 genes, 1 encoding a kinase that phosphorylates ganciclovir and another encoding viral DNA polymerase, appear to facilitate resistance to ganciclovir.[42]

Aciclovir-resistant herpesvirus DNA polymerase mutants are often susceptible to ganciclovir which suggests that the triphosphate salts of the 2 drugs have differing inhibitory effects on DNA polymerase. However, some degree of cross-resistance between ganciclovir and aciclovir has been demonstrated *in vitro*.[43] Drew et al.[39] estimated that 7.6% of 72 patients with acquired immune deficiency syndrome (AIDS)-related cytomegalovirus infection who received >3 months' treatment with ganciclovir were excreting ganciclovir-resistant strains of the virus.

2. Pharmacokinetic Properties

This section is based on the previous review in *Drugs*[1] and presents an overview of the pharmacokinetic profile of ganciclovir supplemented with new data where appropriate.

2.1 Absorption and Plasma Concentrations

2.1.1 Intravenous Administration

The pharmacokinetic properties of intravenous ganciclovir are best described by a 2-compartment open model with mean peak drug concentrations increasing in a linear fashion over a 1 to 5 mg/kg dosage range (reviewed in Faulds & Heel[1]). In transplant recipients, a significant correlation has been demonstrated between administered dose and peak serum ganciclovir concentrations ($r = 0.692$; $p = 0.00009$), but neither dose nor creatinine clearance were correlated with trough serum concentrations.[44] Steady-state peak plasma concentrations after multiple ganciclovir doses are similar to those after equivalent single doses, indicating that accumulation is unlikely in patients with normal renal function.

2.1.2 Oral Administration

A single oral 10 mg/kg dose of ganciclovir solution produced peak plasma concentrations of between 0.23 and 0.35 mg/L in 6 patients approximately 1.5 hours after administration. Bioavailability ranged between 5.4 and 7.1% (mean 6%).[45] Multiple 10 or 20 mg/kg oral doses of ganciclovir produced maximum plasma concentrations of 0.50 and 0.74 mg/L, respectively, between 30 and 60 minutes after administration; minimum plasma concentrations of 0.22 and 0.26 mg/L, respectively, were recorded at 6 hours.[46] Follansbee et al.[47] reported a mean bioavailability of 6% in 8 patients with AIDS and cytomegalovirus retinitis treated with oral ganciclovir capsules 1000mg every 8 hours; a maximum plasma concentration of 0.6 mg/L was achieved 30 to 60 minutes after administration.[46] Administration with food has been shown to enhance the relative bioavailability of oral ganciclovir in patients with AIDS.[48]

2.1.3 Intraocular Administration

Intravitreal injection of ganciclovir 1000μg in 5 divided doses over 15 days produced an immediate intravitreal fluid concentration of 16.25 μg/ml in a patient with AIDS and cytomegalovirus retinitis; the drug was not detected in plasma.[49] Ashton et al.[50] measured the intravitreal pharmacokinetic parameters of sustained-release ganciclovir pellets implanted into the eyes of 8 patients with cytomegalovirus retinitis. Vitreous samples were obtained from 7 of 11 treated eyes after the death of the patient (n = 6) or during ocular surgery (n = 1) between 11 and 70 days after implantation. The mean intravitreal ganciclovir concentration was 2.0 mg/L and the mean release rate was 1.9 μg/h.

2.2 Distribution

Concentrations of ganciclovir in the lung, liver and testes of patients with leukaemia who died from disease complications while receiving the drug intravenously were approximately equal to those found in heart blood. Ganciclovir concentrations in the central nervous system were lower than the mean heart blood concentration but those in the kidney were higher.[51] Cerebrospinal fluid ganciclovir concentrations were 0.68 mg/L when measured 3.5 hours after intravenous administration of a 2.5 mg/kg dose.[52] Laskin et al.[53] reported a cerebrospinal fluid ganciclovir concentration of 0.6 mg/L within 1 hour in a patient given intravenous ganciclovir 1 mg/kg; the corresponding serum ganciclovir concentration was 1.45 mg/L, a penetration rate of 41%.

Case reports available at the time of the previous review[1] reported low ganciclovir concentrations in subretinal fluid 2.5 and 8 hours after intravenous infusions of 5 and 6 mg/kg, respectively.[54,55] More recently, Kuppermann et al.[56] reported a mean intravitreal ganciclovir concentration of 0.96 mg/L. Samples were taken surgically 12 (mean) hours postdose from 23 eyes of 22 patients with AIDS treated with intravenous ganciclovir 6.1 (mean) mg/kg/day.

Reported mean volumes of distribution for intravenously administered ganciclovir at steady-state in patients with normal renal function range between 32 and 44.5 L/1.73m^2.[1] *In vivo* data suggest that ganciclovir is passively transported across the human placenta.[57]

2.3 Metabolism and Elimination

The kidneys are the major elimination route for ganciclovir, with almost 100% of an intravenously administered dose being excreted unchanged in the urine of patients with normal renal function. The elimination half-life ($t_{1/2\beta}$) of intravenous ganciclovir 1 to 5 mg/kg ranges between 2 and 4 hours with a mean clearance rate of 12 L/h/1.73m^2 (200 ml/min/1.73m^2).[1]

Henry et al.[58] reported a $t_{1/2\beta}$ of 13.3 hours for ganciclovir in vitreous fluid after intravitreal administration.

2.3.1 In Patients with Impaired Renal Function

The clearance rate of ganciclovir is directly related to the creatinine clearance rate; thus, the plasma $t_{1/2\beta}$ and maximum plasma concentration of the drug are increased in patients with renal impairment.[52,59] The terminal $t_{1/2\beta}$ of ganciclovir ranged between 9 and 30 hours in patients with a creatinine clearance ranging between 1.2 and 3 L/h/1.73m^2

(20 and 50 ml/min/1.73m^2).[60] Haemodialysis decreases plasma ganciclovir concentrations, removing approximately 50% of a given dose over 4 hours.[1] Lake et al.[61] reported a ganciclovir clearance rate of 4.11 L/h/1.73m^2 (68.5 ml/min/1.73m^2) in a dialysis patient.

Boulieu et al.[62] evaluated the pharmacokinetics of ganciclovir 5 mg/kg administered every 48 hours to 3 anuric heart transplant recipients who were undergoing continuous venovenous haemodialysis. The mean $t_{1/2\beta}$ was 18.9 hours and the average dosage fraction removed by haemodialysis was 89.7%.

2.4 Pharmacokinetics in Neonates and Children

27 neonates (aged 2 to 49 days) with congenital cytomegalovirus infection received a single intravenous dose of ganciclovir 8 (n = 14) or 12 (n = 13) mg/kg. The pharmacokinetic profile of ganciclovir was best described by a single-compartment model, in contrast to that in adults.[63] Jacqz-Aigrain et al.[64] described the pharmacokinetics of ganciclovir in 3 children (aged 9 to 16 years) who developed symptomatic cytomegalovirus infection after renal transplant surgery. The dosage schedule of ganciclovir was reduced according to the degree of renal insufficiency. In all cases plasma ganciclovir clearance was inversely related to creatinine clearance.

3. Therapeutic Use in Cytomegalovirus Infection

Cytomegalovirus infection is normally asymptomatic in immunocompetent individuals, but may cause a variety of clinical syndromes – including retinitis, oesophagitis, colitis, pneumonia, encephalitis or myelitis – in patients with suppressed or deficient immune function.[65] Thus, the majority of studies investigating the clinical efficacy of ganciclovir against cytomegalovirus infection have been conducted in immunocompromised patients, usually those with AIDS or in organ transplant recipients.

3.1 AIDS-Related Cytomegalovirus Retinitis

Cytomegalovirus retinitis is rare in immunocompetent individuals,[66] but occurs in 20 to 30% of adult patients with AIDS.[67] The treatment strategy for cytomegalovirus retinitis in patients with AIDS has been likened to that for a responsive but incurable malignancy where a period of induction therapy is usually followed by life-long reduced-dose maintenance therapy.[65] Because of this, time to recurrence of active disease is often used as the primary measure of therapeutic efficacy.[56,68] The publication of many clinical trials since the previous review in *Drugs*[1] has greatly increased the data available regarding the use of ganciclovir in this indication. Evidence suggests that the availability of ganciclovir and foscarnet has decreased the rate of vision deterioration in patients with AIDS who develop cytomegalovirus retinitis.

Results from many small noncomparative trials suggest that intravenous ganciclovir is an effective treatment for patients with AIDS-related cytomegalovirus retinitis.[69-77] Feinberg et al.[78] reported a mean time to progression of retinitis of 79 days in 701 patients with AIDS-related cytomegalovirus retinitis treated with ganciclovir 5 mg/kg twice daily for 14 days then 35 mg/kg/week indefinitely. In another study, treatment with ganciclovir 7.5 to 10 mg/kg/day for 10 to 21 days then 5 to 10 mg/kg 3 or 5 times/week prevented blindness in at least 1 eye in 57% of 41 patients. Visual deterioration was completely prevented in 24%. Median survival time was 6 months.[79]

One study has evaluated deferment of ganciclovir therapy in patients without immediately sight-threatening retinitis. Spector et al.[80] randomised patients with cytomegalovirus retinitis that was not immediately sight threatening to either immediate [5 mg/kg twice daily (14 days) then 5 mg/kg once daily] or deferred (until progression of retinitis) ganciclovir therapy. Based on photographs, the median time to progression was 49.5 days in 13 patients who received immediate treatment versus 13.5 days in 22 patients in whom treatment was deferred (p = 0.001).

Jordan[81] followed 17 patients with AIDS and elevated cytomegalovirus titres but without cytomegalovirus retinitis at baseline. None of 9 patients who received prophylactic ganciclovir, versus 4 of 8 untreated control patients, developed cytomegalovirus infection.

3.1.1 Combination Therapy

Combination therapy with ganciclovir and cytomegalovirus immune globulin has been shown to be effective in transplant recipients (see section 3.5), but little information is available regarding the use of this combination in patients with AIDS-related cytomegalovirus retinitis, and no consensus regarding its use in this area has yet emerged. One pilot study evaluated the efficacy of 10 days' therapy with intravenous ganciclovir 5 mg/kg every 12 hours combined with intravenous cytomegalovirus immune globulin 400 to 500 mg/kg administered on days 1 to 3 and 400 mg/kg on days 8 to 10 in 6 such patients. Of these, 4 received maintenance therapy with intravenous cytomegalovirus immune globulin 400 mg/kg once every 14 days. Median time to retinitis progression was shorter in the combination therapy group than in 8 historical control patients who received maintenance therapy with ganciclovir (7 *vs* 54 days; p = 0.06) and a further group of 8 historical control patients who received ganciclovir for 10 days only (19 days; p = 0.97).[82] In contrast, a more recent prospective randomised comparison found combination therapy with ganciclovir and cytomegalovirus immune globulin prolonged the median time to progression of retinitis (to 159 days; n = 9) compared with ganciclovir monotherapy (to 89 days; n = 7).[83]

The thymidine analogue zidovudine is able to delay disease progression, reduce opportunistic infections and increase survival in patients with ad-

Table II. Trials evaluating the efficacy of combination intravenous therapy with ganciclovir (GCV) and foscarnet (PFA) in patients with acquired immune deficiency syndrome and cytomegalovirus retinitis and/or gastrointestinal infection

Reference	No. of patients (retinitis : gastrointestinal infection)[a]	Induction regimen		Maintenance regimen		No. of patients with complete or partial response [% of patients]
		dosage (mg/kg/day)	duration	dosage (mg/kg/day)	duration (weeks)	
Dieterich et al.[91]	10 (9 : 5)	–[b]	median 330 days	GCV 10 PFA 180	1-27	9 [90]
Flores-Aguilar et al.[93]	4 (4 : 0)[c]	GCV 5 PFA 180	2-3 weeks	GCV 5 PFA 90-120	5-33	3 (5/8 eyes) [75]
Kuppermann et al.[90]	7[d] (9 : 0)[c]	GCV 5-10 PFA 90-180	2-4 weeks	GCV 5-10 PFA 90-180	4-32	7 (14/14 eyes) [100]
Peters et al.[95]	10 (7 : 5)[e]	GCV 10[f] PFA 180	3 weeks	GCV 5 q2d PFA 120 q2d	5-51	7 [70]
Salzberger et al.[94]	13 (7 : 7)	GCV 5 mg/kg bid + PFA 90 mg/kg bid for 3 weeks[g]				12/14 episodes [86]
Stoehr et al.[92]	16 (12 : 4)[h]	GCV 5 PFA 90	14-37 days			15 [94][i]

a Some patients had both retinal and gastrointestinal infection.

b Patients received ganciclovir and/or foscarnet monotherapy before commencing combination therapy because of lack of response to monotherapy.

c All with retinitis resistant to monotherapy with ganciclovir and/or foscarnet.

d A further 2 patients were noncompliant and were given monotherapy at their request. One of these patients subsequently relapsed while the other had a partial response.

e None had received prior anticytomegalovirus treatment.

f Five patients received induction therapy with ganciclovir only.

g The duration of this study was fixed and neither maintenance or induction therapy *per se* were given.

h This was the first episode of cytomegalovirus infection in 3 patients and a relapse in the remainder.

i At the end of induction therapy.

Abbreviations: bid = twice daily; q2d = every second day, i.e. the 2 drugs were given on alternate days.

Table III. Trials comparing intravenous therapy with ganciclovir (GCV) or foscarnet (PFA) in patients with previously untreated acquired immune deficiency syndrome-related cytomegalovirus retinitis

Reference	Drug (no. of patients entered)	Study design	Induction regimen (mg/kg) [duration in weeks]	Maintenance regimen (mg/kg) [duration in weeks]	Complete response rate at the end of induction therapy (evaluable patients) [%]	No. of patients relapsing during maintenance (mean time to reactivation)
LeHoang et al.[96]	GCV (32)	pl	NR [3]	NR [12]	28/32 [87]	12/12[a] (6 weeks)
	PFA (40)		NR [3]	NR [12]	35/40 [87]	4/12[a] (12 weeks)
Moyle et al.[97]	GCV (26)	r, nm, pl	5 bid [3]	5 od 5 days/week	19/22 [86]	6 (25 weeks)
	PFA (31)		130-200[b] [3]	120 od 5 days/week	17/25 [68]	7 (14 weeks)
SOCA & ACTG[98]	GCV (127)	mc, r, nm, pl	5 q12h [2]	5 od		9[c] (8 weeks)
	PFA (107)		60 q8h [2]	90 or 120 od		9[c] (8.4 weeks)

a Evaluable patients.

b Initial loading dose of 20 mg/kg followed by either 16-hour infusions or three 2-hourly infusions.

c The number of patients who switched from one treatment to the other because of progression; overall progression rates were not presented.

Abbreviations: ACT = AIDS Clinical Trials Group; bid = twice daily; mc = multicentre; nm = nonmasked; NR = not reported; od = once daily; pl = parallel; q8h = every 8 hours; q12h = every 12 hours; r = randomised; SOCA = Studies of Ocular Complications of AIDS research group.

vanced human immunodeficiency virus (HIV) infection, but has been associated with haematological toxicity.[84] Millar et al.[73] treated patients with AIDS-related cytomegalovirus retinitis with ganciclovir monotherapy (n = 9) or ganciclovir plus zidovudine (n = 7). The 2 regimens were equally effective in terms of vision outcome but combination therapy recipients had significantly ($p < 0.05$) greater transfusion requirements than monotherapy recipients. Moreover, Hochster et al.[85] reported haematological toxicity in 82% of 41 patients receiving this combination.

Several case reports suggest that combination therapy with ganciclovir and foscarnet may be effective in patients unable to tolerate either drug as monotherapy or in those with progressive infection despite optimal monotherapy.[86-89]

Results from a number of pilot studies[90-95] involving patients with AIDS-related cytomegalovirus retinitis and/or gastrointestinal infection have also been favourable (table II). In one of these trials[92] ganciclovir and foscarnet were each given at half the normal daily dose. In another, the 2 drugs were given on alternate days.[95]

3.1.2 Comparisons with Foscarnet

Few studies have compared the efficacies of ganciclovir and foscarnet in patients with AIDS-related cytomegalovirus retinitis and none have demonstrated any significant difference between the 2 treatments in terms of efficacy (table III).[96] Moyle et al.[97] intended to enrol 130 patients but halted their study after an interim analysis indicated that detection of a significant difference between the 2 drugs would be unlikely. Although the larger Studies of Ocular Complications of AIDS research group (SOCA) and AIDS clinical trials (ACTG) trial[98] also reported ganciclovir and foscarnet to be similarly effective, the mortality rate was significantly higher in ganciclovir recipients than in foscarnet recipients (see section 3.1.4).

3.1.3 Alternatives to Intravenous Maintenance Therapy

Problems associated with intravenous administration of ganciclovir, notably dose-related bone marrow suppression and neutropenia (see section 4), catheter infections and sepsis, and the difficulties that can occur when ganciclovir and zidovudine are administered concurrently (see section 5), can necessitate the temporary or permanent with-

drawal of intravenous ganciclovir maintenance therapy. Several alternative methods of administering the drug have therefore been investigated.

Oral Therapy

Preliminary results from studies comparing the efficacies of oral and intravenous ganciclovir maintenance therapy are now available. Two studies compared treatment with oral ganciclovir 3000 mg/day and intravenous ganciclovir 5 mg/kg/day. In the first, patients with stable retinitis after 3 weeks' intravenous ganciclovir induction therapy were enrolled and commenced a 20-week course of oral (n = 60) or intravenous (n = 57) maintenance therapy. Measured by fundoscopy, the mean time to progression was 68 days in recipients of oral ganciclovir versus 96 days in intravenous ganciclovir recipients. Mean time to progression was similar when measured using photographs (57 *vs* 62 days). There was no significant difference between intravenous and oral ganciclovir in the time from the start of maintenance therapy to deterioration of visual acuity.[99] The second study randomised 159 patients 2 : 1 to oral or intravenous ganciclovir. Measured by fundoscopic evaluation the mean time to progression was 109 days in the intravenous group versus 86 days in the oral group.[100] A further trial compared maintenance therapy with oral ganciclovir [either 500mg 6 times daily (n = 72) or 1000mg 3 times daily (n = 76)] with intravenous ganciclovir 5 mg/kg/day (n = 68). Mean time to progression measured by indirect ophthalmoscopy was 98 days in intravenous ganciclovir recipients versus 73 and 76 days in those receiving 6 and 3 daily oral doses, respectively.[101]

Intravitreal Injection, Implants and Liposomal Encapsulation

At the time of the previous review in *Drugs*[1] there was some indication from the literature that intravitreally injected ganciclovir might have a place in the treatment of patients with AIDS-related cytomegalovirus retinitis in whom intravenous administration of the drug is not feasible. Since that time, further studies have been published, some involving relatively large numbers of patients. All of these larger trials reported good response rates to intravitreal induction therapy, and progression rates during maintenance therapy were similar to those observed in studies investigating intravenous therapy (table IV).[102-104]

However, the requirement for repeated injections when ganciclovir is administered intravitreally has led to the development of controlled-release intravitreal formulations. Two approaches have been used: liposomal encapsulation and intravitreal implants. Liposomal formulations have the potential to allow controlled release of an encapsulated drug while avoiding high concentration peaks. After obtaining favourable results from studies in rabbits, Diaz-Llopis et al.[109] administered liposomally encapsulated ganciclovir to 5 patients with unilateral AIDS-related cytomegalovirus retinitis. Liposomes containing a total ganciclovir dose of 0.5mg were injected intravitreally once weekly for 3 weeks and every 15 days thereafter. Complete remission occurred in all 5 patients during induction therapy and was maintained during 2 to 4 months' follow-up.

A further pilot study evaluating the efficacy of an unspecified intraocular implant in patients with AIDS-related cytomegalovirus retinitis reported regression in 18 of 20 (90%) patients intolerant of intravenous treatment.[110]

3.1.4 Survival

The SOCA and ACTG trial[98] found ganciclovir and foscarnet to be similar in terms of efficacy but the relative risk of mortality was higher in patients who received ganciclovir than in those who received foscarnet [observed relative risk (RR) 1.77, p = 0.007; adjusted RR 1.79; p = 0.006]. Median survival times were 8.5 and 12.6 months in the ganciclovir and foscarnet groups, respectively. Possible reasons for this difference include the *in vitro* activity of foscarnet against human immunodeficiency virus and the poorer tolerability of zidovudine in ganciclovir compared with foscarnet recipients, with the latter possibly receiving more effective antiretroviral therapy be-

Table IV. Recent studies evaluating the use of intravitreal injections of ganciclovir (GCV) as treatment for human cytomegalovirus (CMV) retinitis in patients with acquired immune deficiency syndrome

Reference	No. of patients (eyes)	Ganciclovir dosage		Response to induction	Clinical relapse/ disease progression during maintenance	Comments
		induction (duration)	maintenance			
Cochereau-Massin et al.[102]a	95 (137)	400μg biw (mean 3 weeks)	400 μg/week until relapse	Cicatrization occurred after 123/133 courses	10-week relapse rate was 53%	Unilateral retinitis progressed to bilateral retinitis in 7% of patients
Heinemann[72]	7 (13)	1200μg in 6 divided doses (18 days)	200 μg/week indefinitely	Stabilisation of retinitis in all patients	2/5 patients relapsed after 10 and 15 weeks' treatment	Despite ophthalmoscopic evidence of improvement, visual acuity deteriorated in all but 1 patient during follow-up
Hodge et al.[105]	40 (64)		400 μg/week		Progression in 39/57 eyes after 23.7 (mean) weeks	Retrospective study of maintenance therapy
Lieberman & Orellana[104]	44 (46)	400μg (no further details given)	400μg (no further details given)		Successful resolution in 40 eyes	Reactivation occurred in 36 eyes following resolution
Orduna et al.[107]	4 (5)	200μg biw (1 month)	200 μg/week indefinitely		Infection remitted in all eyes	Infection recurred in 2 patients after temporary withdrawal of GCV
Orellana et al.[106]	5 (8)	200μg q5d (15 days)	200 μg/weekb		Nil	Intravitreal therapy alone did not improve CMV retinitis
Polsky et al.[108]	8 (12)	200μg biw	200μg	All of 10 evaluable eyes responded	Progression occurred in 3 eyes after 7.5 (mean) weeks	3 patients developed extraocular CMV disease after 7 (mean) weeks

a Some methodology data from Cochereau-Massin et al.[103]

b Continued until intravenous ganciclovir therapy could be resumed.

Abbreviations: biw = twice weekly; q5d = every 5 days.

cause of this. Indeed, in a letter to the editor after the publication of the SOCA and ACTG trial, Skolnik et al.[111] argued that only 5% of ganciclovir recipients received full doses of zidovudine versus 30% of those who received foscarnet and that 66 versus 84% received some antiretroviral therapy. However, although the SOCA and ACTG[98] trial found no significant differences in the patterns of mortality when results were analysed according to concomitant drug use, mortality tended to be higher in ganciclovir recipients regardless of antiretroviral treatment. Skolnik et al.[111] also pointed out that 39 of 107 patients initially treated with foscarnet were switched to ganciclovir [primarily because of drug-related toxicity (22 of 39)] and 14 of 127 initially treated with ganciclovir were switched to foscarnet [primarily because of progression of retinitis (9 of 14)]. In contrast to the results of the SOCA and ACTG trial, an earlier retrospective study found similar survival rates in 168 patients with AIDS-associated cytomegalovirus retinitis treated with ganciclovir or foscarnet.[112]

Bertoni et al.[113] studied the relationship between response to treatment with ganciclovir and survival in patients with AIDS-related cytomegalovirus retinitis. Progression of retinitis occurred in 6 of 38 patients; these patients survived for 27.1 days. 24 of 32 patients who responded to treatment died after 73.3 (mean) days; the remaining 8 patients were still alive at the end of the study. Furthermore, a retrospective review of 100 patients with AIDS-related cytomegalovirus retinitis found that patients treated with ganciclovir lived longer

(median 7 months) after diagnosis of cytomegalovirus retinitis than untreated patients (median 2 months).[114]

3.2 AIDS-Related Gastrointestinal Cytomegalovirus Infection

After the retina, the gastrointestinal tract is the most common site of cytomegalovirus infection in patients with AIDS.[115] Estimates of the prevalence of AIDS-related gastrointestinal cytomegalovirus infection range between 10.3%[115] and 30%.[116] Few trials have been conducted to assess the efficacy of ganciclovir as treatment for this condition; nevertheless, results from 2 non-comparative studies conducted solely in this indication suggest that the drug may be useful.[117,118] Results from further studies including patients with gastrointestinal and/or retinal cytomegalovirus infection are also favourable (table II). A double-blind randomised placebo-controlled study undertaken to confirm these preliminary findings reported treatment with ganciclovir 5 mg/kg twice daily for 14 days to be beneficial in patients with biopsy-proven cytomegalovirus colitis. Treatment was considered successful – defined as completion of the study and improved colonic histology – in 20 of 32 (62.5%) ganciclovir versus 11 of 30 (36.7%) placebo recipients ($p = 0.042$).[119] Results from a further randomised double-blind in 36 patients with acute AIDS-related cytomegalovirus gastrointestinal infection trial suggest that a lower 1 mg/kg twice daily ganciclovir dose is as effective as 5 mg/kg twice daily (symptom improvement in 93 *vs* 94% of patients).[120]

3.3 AIDS-Related Cytomegalovirus Pneumonia

The primary manifestation of pulmonary cytomegalovirus infection is interstitial pneumonia.[65] Treatment with ganciclovir is less effective in this indication than in cytomegalovirus retinitis with approximately 50 to 60% of patients responding to an initial course (reviewed in Drew[65]). The drug is generally given at a dose of 5 mg/kg twice daily and may be withdrawn once the pneumonia has resolved.[65]

Limited data available at the time of the previous review[1] indicated that induction therapy with ganciclovir is generally effective in patients with AIDS-related cytomegalovirus pneumonia but was not as effective as treatment for relapse.

3.4 Post-Transplant Cytomegalovirus Infection

The transplanted organ and surrounding structures are the most frequent sites of post-transplantation cytomegalovirus infection. Cytomegalovirus may be transmitted to transplant recipients via infected donor organs or cellular blood products; the allograft is the primary source of cytomegalovirus infection after solid organ transplantation.[121] Reactivation of latent virus is another potential source of infection and may be induced by either immunosuppression or allograft rejection.[121] Cytomegalovirus infection occurs in approximately 50 to 75% of patients who undergo solid organ transplantation and is clinically significant in approximately 10 to 30% of patients (reviewed in Dunn & Najarian[122]). It occurs primarily during the first post-transplantation months, when immunosuppressive therapy is most intense.[122] Patients identified as being at high risk of developing cytomegalovirus infection after transplantation are candidates for prophylactic ganciclovir.[123] Ganciclovir has been evaluated as treatment for established symptomatic cytomegalovirus infection, as prophylaxis against infection and, more recently, as treatment for asymptomatic infection.

3.4.1 Treatment of Established Symptomatic Infection

A number of studies have evaluated the efficacy of ganciclovir as treatment for established cytomegalovirus infection in recipients of organ transplants. Ganciclovir either alone[124-126] or in combination with corticosteroids[127] has not proven efficacious as treatment for cytomegalovirus pneumonia in bone marrow transplant recipients. Indeed, ganciclovir appeared to be no more effective

than placebo in terms of overall mortality in 1 randomised double-blind trial.[126] Combination treatment with ganciclovir and cytomegalovirus immune globulin improved survival in bone marrow transplant recipients at some centres[128-131] but not others.[132,133] Results from studies in solid organ transplant recipients are more encouraging. Several studies have reported that monotherapy with ganciclovir is an effective treatment for symptomatic cytomegalovirus infection in renal,[134-138] liver,[139,140] and heart and/or lung transplant recipients[141-143] (table V).

3.4.2 Early Treatment of Asymptomatic Infection

The occurrence of symptomatic cytomegalovirus infection in conjunction with steroid-resistant rejection in transplant recipients can pose a serious therapeutic dilemma. The use of immunosuppressive drugs to counter rejection increases the risk of cytomegalovirus disease; however, withholding these drugs will almost certainly result in the loss of the transplanted organ.[144] A potential solution to this problem is pre-emptive antiviral treatment at the first indication of cytomegalovirus infection, made possible by newer assay methods allowing rapid identification of cytomegalovirus infection.[145] A number of studies have evaluated the efficacy of ganciclovir as early treatment for asymptomatic cytomegalovirus infection in bone marrow transplant recipients. Favourable results from pilot studies[146-149] are supported by the findings of 2 randomised controlled studies[151,152] (table VI). Van Son et al.[144] found pre-emptive treatment with ganciclovir (5 mg/kg twice daily adjusted according to renal function) prevented symptomatic cytomegalovirus infection in 6 of 8 renal transplant recipients with asymptomatic cytomegalovirus infection who were receiving antithymocyte globulin for steroid-resistant rejection. The remaining 2 patients developed minor symptoms of infection. Using a slightly different approach, Singh et al.[154] compared high dose aciclovir prophylaxis with pre-emptive ganciclovir therapy in liver transplant recipients. Initially patients were randomised to no treatment or aciclovir 800mg four times a day and monitored for cytomegalovirus shedding. When cytomegalovirus shedding was detected in untreated patients ganciclovir was started either as pre-emptive therapy (5 mg/kg for 7 days) in the absence of symptomatic cytomegalovirus infection or as treatment (14 to 21 days) when cytomegalovirus disease was diagnosed. Aciclovir recipients who developed cytomegalovirus disease were treated with ganciclovir for 14 to 21 days after which time aciclovir prophylaxis was resumed. Cytomegalovirus shedding was detected with similar frequency in both groups; however, symptomatic cytomegalovirus infection was significantly more frequent in aciclovir recipients versus patients given pre-emptive ganciclovir therapy (29 *vs* 4%; $p < 0.05$).

3.4.3 Prophylaxis

Many studies have evaluated the use of ganciclovir as prophylaxis against cytomegalovirus infection in liver, lung, bone marrow, heart and kidney transplant recipients (table VII).

Liver Transplant Recipients

A retrospective analysis identified 116 cases of cytomegalovirus infection among 444 liver transplant recipients.[155] Despite treatment with ganciclovir these patients experienced a higher rate of early rejection than the 278 patients who did not develop cytomegalovirus infection (78.2 *vs* 47.3%; $p \leq 0.0001$). Bacterial and fungal infections were significantly more prevalent in patients who developed cytomegalovirus infection as were requirements for muromonab CD3 treatment for steroid rejection, and tacrolimus rescue. The retransplant rate in patients who developed cytomegalovirus infections was twice that in those who did not, although this difference was not statistically significant. These findings suggest that ganciclovir prophylaxis may reduce morbidity to a greater extent than treatment with the drug after cytomegalovirus infection has become established.[155] However, a randomised, prospective trial found no significant difference between prophylactic and therapeutic use of ganciclovir after liver transplantation.[156] 65 patients were enrolled; 33 received

Table V. Recent trials evaluating the use of ganciclovir (GCV) as treatment for established cytomegalovirus (CMV) infection in organ transplant recipients

Reference	No. of patients	Diagnosis of CMV infection	Ganciclovir dosage (duration)	Outcome
Renal transplant recipients				
Buturovic-Ponikvar et al.[136]	12	Otherwise unexplained fever, hepatitis or pneumonitis	1.25-5 mg/kg q12h[a]	10/12 patients survived; of these 2 required treatment with anti-CMV globulin
de Koning et al.[137]	13		1.5-10 mg/kg/day od or bid[a]	All patients, including 5 receiving antirejection therapy, responded to GCV
Guerin et al.[135]	11	Otherwise unexplained fever, leucopenia, hepatitis, pneumonitis or GI symptoms	1.25-5 mg/kg/day od or q12h[a]	Defervescence occurred in 8/11 patients after a single course of GCV. 2 patients remained febrile but recovered. Recurrence of fever and GI symptoms in the remaining patient responded to a second course of GCV
Jordan et al. [134]	36	Otherwise unexplained fever, leucopenia, thrombocytopenia and/or diffuse pulmonary infiltrates	1.25-5 mg/kg/day od or q12h[a]	CMV-associated symptoms resolved in all 36 patients
Nicholson et al.[138]	12	Life-threatening or severe CMV pneumonitis or viraemia	5 mg/kg bid (≤14 days)	10/12 patients survived with functional grafts. Defervescence attained after 10.1 (mean) days' treatment. One patient with unresponsive CMV pneumonia died. The second death was caused by acute pancreatitis
Heart and/or lung transplant recipients				
Cerrina et al.[141]	21 (HL or L)		10 mg/kg/day (15 days)	20/21 patients survived initial CMV infection; 1 died of diffuse pulmonary aspergillosis during treatment. 15 patients underwent bronchoscopic examination 15-20 days after the initiation of GCV; 6 had positive results and the duration of GCV treatment was extended in 2 of these. Early CMV recurrence [18 (mean) days after cessation of GCV] in 7 patients. Late recurrence (69-630 days after cessation of GCV) in 4 patients
Cooper et al.[142]	22 (H)		5 mg/kg bid [2-8 (mean 3.5) weeks]	Initial infection resolved in all patients but recurrence was observed in 1 patient. No deaths were definitely attributable to CMV infection
Mullen et al.[143]	14 (H)		15 mg/kg/day (14 days)	CMV infection resolved in 12/14 patients who remained alive 1-33 months after receiving the drug; 2 patients died from stroke or glioblastoma
Liver transplant recipients				
Sanchez-Turrión[140]	7	Fever, leucopenia, GI symptoms	5 mg/kg q12h 3-52 (mean 16.1) days	6/7 patients cured. 1 died from bacterial sepsis and hepatic failure
Bone marrow transplant recipients				
Aulitzky et al.[125]	5	Life-threatening CMV infection	2.5 mg/kg q8h until resolution of CMV-related symptoms[b]	4 patients, 1 of whom had SLE, with CMV pneumonitis requiring mechanical ventilation, died from disseminated CMV infection 3-13 (median 8) days after initiation of therapy. CMV infection resolved in the remaining patient, who did not require mechanical ventilation

Table V. Contd

Reference	No. of patients	Diagnosis of CMV infection	Ganciclovir dosage (duration)	Outcome
Reed et al.[126]c	18	Biopsy-documented CMV GI infection	2.5 mg/kg q8h (14 days)	Cessation of oropharyngeal and urinary CMV excretion, and negative repeat oesophageal cultures significantly more frequent in GCV *vs* placebo recipients ($p < 0.005$). No difference in clinical symptoms or endoscopic appearance between groups at the end of treatment
	19		Placebo	

a Adjusted according to renal function; 3 patients received anticytomegalovirus globulin.

b All patients also received intravenous hyperimmunoglobulin 20g on alternate days.

c Randomised, double-blind trial.

Abbreviations: bid = twice daily; GI = gastrointestinal; L = lung transplant; H = heart transplant; HL = heart-lung transplant; od = once daily; q8h = every 8 hours; q12h = every 12 hours; SLE = systemic lupus erythematosus.

prophylactic ganciclovir 10 mg/kg/day during the third and fourth weeks post-transplant and 32 were given the drug only on diagnosis of clinical cytomegalovirus infection. The incidence of serologically diagnosed secondary infection and development of anti-cytomegalovirus antibody was lower in those who received prophylactic ganciclovir (7/33 *vs* 13/32) but the prevalence of clinical cytomegalovirus infection was similar in both groups (9 *vs* 11).

The use of muromonab CD3 has been identified as an important risk factor for the development of cytomegalovirus infection in liver transplant recipients.[157,158] Lumbreras et al.[159] evaluated the efficacy of intravenous ganciclovir 5 mg/kg every 12 hours for 14 days as prophylaxis against cytomegalovirus infection in 25 liver transplant recipients receiving muromonab CD3 5 mg/day intravenously for ≥7 days. Three of 25 (12%) ganciclovir recipients developed active cytomegalovirus infection compared with 13 of 25 (52%) patients in a historical control group.

Lung Transplant Recipients

Cytomegalovirus infection is a particular problem in recipients of lung transplants; the organism commonly infects the transplanted organ and causes considerable morbidity and mortality. Interventions to prevent cytomegalovirus infection in these patients include matching seronegative transplant recipients to seronegative donor organs and administration of cytomegalovirus hyperimmune globulin. Pilot studies investigating the efficacy of ganciclovir prophylaxis against cytomegalovirus infection in lung transplant recipients have produced conflicting results but generally show little effect (table VII).[160-163]

Bone Marrow Transplant Recipients

Interstitial pneumonia caused by cytomegalovirus infection is a frequent and often fatal complication of allogeneic bone marrow transplantation. A number of risk factors for cytomegalovirus pneumonia in allogeneic bone marrow transplant recipients have been identified, including seropositivity (RR = 2.9); conditioning with total-body irradiation (RR = 2.7); advancing age (RR = 1.4 per decade); receipt of antithymocyte globulin (RR = 2.9); T cell-depleted bone marrow (RR = 2.7); and cytomegalovirus viuria (RR = 7.0) or viraemia (RR = 15.4).[164] Similar relative risks were reported in an earlier study.[165]

Comparisons with placebo have demonstrated prophylactic ganciclovir therapy to reduce the incidence of cytomegalovirus interstitial pneumonia in bone marrow transplant recipients.[166-168]

3.4.4 Cytomegalovirus Infection in Paediatric Transplant Recipients

Studies have evaluated the use of ganciclovir both as prophylaxis against and treatment for cyto-

megalovirus infection in children who have received liver transplants.

Ganciclovir alone (5 mg/kg twice daily for 14 days) was as effective as initial administration of ganciclovir followed by oral aciclovir (800 mg/m^2 4 times daily until 1 year post-transplant) as prophylaxis against cytomegalovirus infection in children who had undergone liver transplantation. Cytomegalovirus infection occurred in 3 of 10 children who received ganciclovir then aciclovir versus 2 of 19 who received ganciclovir monotherapy.[170] Ganciclovir 5 mg/kg twice daily for 14 days resolved infection in 11 of 12 children who developed cytomegalovirus infection after undergoing liver transplantation.[171] The remaining patient died from cytomegalovirus pneumonitis refractory to treatment. Three patients in whom treatment was initially successful had recurrence of cytomegalovirus infection; of these, 2 responded to retreatment whereas infection was asymptomatic in the third patient and was not treated.

A further study compared ganciclovir prophylaxis with ganciclovir treatment in children who had undergone renal transplantation. 10 children seropositive for anticytomegalovirus immunoglobulin prior to transplant received prophylactic ganciclovir 10 mg/kg/day adjusted according to renal function; clinical symptoms occurred in 3. In contrast, clinical symptoms developed in 10 of 24 children who did not receive prophylactic

Table VI. Trials evaluating the use of intravenous ganciclovir (GCV) as early treatment for cytomegalovirus (CMV) infection in bone marrow transplant recipients

Reference	No. of patients	Criteria for initiation of GCV treatment	Ganciclovir regimen (duration)	Outcome
Atkinson et al.[149]	25	CMV seropositive	5 mg/kg bid between 8 days and 1 day pretransplant then from 21 days post-transplant[a]	No episodes of CMV disease occurred
Bacigalupo et al.[146]	24	Expression of the lower matrix protein pp65 of CMV on peripheral blood cells and urine sediments	10 mg/kg/day (21 days) then twice weekly[b]	Infection cleared in 21 patients but 4 died. Mortality rate was 18% in GCV recipients *vs* 42% in an untreated control group
Goodrich et al.[151][c]	72	Detection of CMV post-transplant	5 mg/kg bid (1 week) then 5 mg/kg/day until 100 days post-transplant	1/37 GCV *vs* 15/35 placebo recipients developed CMV infection ($p < 0.00001$)
Lehn et al.[153]	18	Isolation of CMV from BAL	5 mg/kg bid (20 days) then od 3/7 days[d]	Nine patients without pulmonary symptoms became long term survivors. Of the 9 deaths, 2 were related to CMV pneumonia
Milpied et al.[148]	6 (pilot study)	CMV viraemia	2.5 mg/kg tid (20 days)	CMV viraemia resolved in all patients but 1 patient who developed neutropenia after treatment with GCV died from disseminated aspergillosis
	10	CMV viraemia	5 mg/kg bid (15 days)	Viraemia resolved in all patients but recurred in 8 after cessation of GCV
Schmidt et al.[152]	33	Asymptomatic pulmonary CMV infection	GCV 5 mg/kg bid (2 weeks) then 5 mg/kg od 5/7 days (106 days)	CMV disease occurred in 4/18 (22%) GCV recipients *vs* 10/15 (67%) untreated patients

a Ganciclovir was not restarted unless the neutrophil count exceeded 1×10^9/L.

b All patients received biweekly intravenous immunoglobulin 200mg.

c Randomised double-blind placebo-controlled study.

d All patients received immunoglobulin 500 mg/kg every second day (19 days) then twice weekly (8 doses).

Abbreviations: BAL = bronchoalveolar lavage; bid = twice daily; IVIG = intravenous immunoglobulin; od = once daily; tid = 3 times daily.

Table VII. Efficacy of intravenous ganciclovir (GCV) as prophylaxis against cytomegalovirus (CMV) infection in organ transplant recipients

Reference	Design	Patient selection criteria	Treatment regimen	Rate of CMV infection
Bone marrow transplant				
Goodrich et al.[166]	r, db, pc, pl	CMV seropositive	GCV 5 mg/kg bid (5 days) then od (95 days)	1/33 (3%)
			Placebo	14/31 (45%)*
Von Bueltzingsloewen et al.[167]	Untreated historical control group comparison	CMV seropositive recipient or donor	GCV 6 mg/kg 10-4 days before transplantation (CMV seropositive patients); day 30 - day 90 post-transplant (all patients)	1/40 (2.5%)
			No treatment	23/39 (59%)
Winston et al.[168]	r, db, pl	CMV seropositive	GCV 2.5 mg/kg q8h for 1 week prior to transplant then 6 mg/kg/day 5 days/week thereafter	8/40 (20%)
			Placebo	25/45 (56%)**
			No treatment	15/30 (50%)
Yau et al.[150]	Untreated historical control group comparison	CMV seropositive	GCV 2.5 mg/kg q8h for 1 week prior to transplant then aciclovir and IVIG[a] then GCV 6 mg/kg/day 3/7 days until 70 days post-transplant[b]	3/14 (21%)
			No treatment	15/30 (50%)
Renal transplant				
Rondeau et al.[169]	r, nb, pl	CMV seronegative recipients of kidneys from seropositive donors	GCV 5 mg/kg bid (14 days starting on the 14th post-transplant day)	12/17 (70.6%)
			No treatment	12/15 (80%)
Heart transplant				
Merigan et al.[162]	mc, r, db, pc	CMV seropositive recipient or donor	GCV 5 mg/kg q12h from day 1-14 post-transplant then 6 mg/kg 5/7 days (2 weeks)	Seropositive 5/56 (9%) Seronegative (35%)
			Placebo	Seropositive 26/56 (46%)*** Seronegative (29%)
Lung transplant				
Duncan et al.[161]	nc	CMV seropositive recipient or donor	GCV 5 mg/kg bid [14 days (from 7 days post-transplant)] then 5 mg/kg/day (1 week)[b]	5/13 (38%)
Ladurie et al.[160]	Historical control group	CMV seropositive recipient or donor	GCV 10 mg/kg/day between 15 and 30 days post-transplant	6/7 (86%)
			No treatment	23/23 (100%)
Schmuth et al.[163]	Untreated control group comparison	NR	GCV 10 mg/kg/day for 1-10 days post-transplant	6/7 (86%)
			No treatment	6/7 (86%)

a Intravenous aciclovir 5 mg/kg was given every 8 hours from the first post-transplant day until the absolute granulocyte count exceeded 500×10^6/L and the platelet count reached 20×10^9/L without requirement for platelet transfusion. IVIG 500 mg/kg was given once every 2 weeks between 2 days pre- and 250 days post-transplant. Oral aciclovir 200 mg/day was given between 70 days and 1 year post-transplant.

b Adjusted according to renal function.

c After completing ganciclovir therapy all patients received aciclovir 800mg 3 times daily for ≥2 months.

Abbreviations and symbols: bid = twice daily; db = double-blind; mc = multicentre; nb = nonblind; nc = noncomparative; nr = not reported; od = once daily; pc = placebo comparison; pl = parallel; q8h = every 8 hours; q12h = every 12 hours; q2w = every 2 weeks; r = randomised; * $p < 0.001$ *vs* ganciclovir; ** $p < 0.01$ *vs* ganciclovir; *** $p < 0.001$ *vs* seropositive ganciclovir group.

ganciclovir; pneumonia developed in 2 children, 1 of whom died.[172]

3.5 Congenital Cytomegalovirus Infection

Fewer than 25% of infants congenitally infected with cytomegalovirus develop symptoms. Symptomatic congenital cytomegalovirus infection is often fatal, however, and permanent sequelae can occur in 90 to 95% of survivors.[66,173] A number of investigators have published case reports and case series documenting the use of ganciclovir as treatment for congenital cytomegalovirus infection.[174-179] Most administered ganciclovir 5 mg/kg every 12 hours for 14,[174,175,177], 21[180] or 25[177] days, although Tricoire et al.[179] used 10 to 15 mg/kg/day for 10 to 20 days and Junker et al.[178] used 7.5 mg/kg/day in 3 divided doses for 14 days then 5 mg/kg every second day for a further 14 days. Outcome was not favourable in the majority of cases. Viral shedding almost invariably recurred after cessation of ganciclovir therapy despite being eliminated during treatment. Although only 2 of a total of 12 infants died, 6 had neurological sequelae. Coadministration of intravenous immunoglobulin had no apparent effect on outcome. Interestingly, outcome appeared to be more favourable in those infants treated for longer periods of time.[177,179] Results from a pilot study support this finding: ganciclovir at a dosage of 5 mg/kg twice daily for 2 weeks was not as effective as 7.5 mg/kg twice daily for 2 weeks then 10 mg/kg 3 times weekly for 3 months. Normal outcome was observed in 2 of 6 infants with congenital cytomegalovirus infection who received the shorter regimen compared with 5 of 6 who received extended treatment.[173]

4. Tolerability

As discussed in the previous review[1] and by DeArmond[181], it is difficult to clearly determine the tolerability profile of ganciclovir, since the underlying immunological compromise in most of those who receive the drug can be symptomatic. Additionally, many ganciclovir recipients are also receiving a number of other medications and may also have polymicrobial infection. Indeed, most data regarding the adverse effect profile of ganciclovir have been obtained during a compassionate-use programme involving immunosuppressed patients with life- or sight-threatening cytomegalovirus infection.[181] Ethical considerations are likely to preclude the initiation of placebo-controlled trials further confounding objective evaluation of the drug's tolerability profile.

4.1 Haematological Toxicity

Concentrations of ganciclovir equivalent to those achieved clinically inhibit the growth of human bone marrow colony-forming cells *in vitro*.[36,182,183] Neutropenia – defined as a >50% decrease in absolute neutrophil count from baseline or <1000 neutrophils/μl – is the most common adverse event in patients treated with ganciclovir. Neutropenia has been the only adverse effect attributable to ganciclovir in a number of studies[1] and was the most common adverse event in a large noncomparative trial evaluating the efficacy of ganciclovir as treatment for AIDS-related cytomegalovirus retinitis. 1125 patients were enrolled and 828 were available for evaluation of tolerability. 48 withdrew because of adverse events (which were not specified in the abstract report).[78] Ganciclovir-associated neutropenia appears to be dose related – generally occurring before a total cumulative dose of 200 mg/kg has been given – but can occur at any time during therapy.[1] The overall incidence of this adverse effect in patients enrolled in the compassionate-use treatment programme was 38%[181] and was dose-limiting (absolute neutrophil count <500/μl) in approximately 16%. Patients with AIDS appeared to be at greater risk of developing neutropenia than other patient groups but often received longer courses of therapy. The pretreatment neutrophil count or the ganciclovir dosage regimen selected do not appear to be predictive of the occurrence of neutropenia, although initiation of ganciclovir treatment is not recommended in patients with an absolute neutrophil count below 500/μl.[1]

Overall, approximately 20% of ganciclovir recipients experience thrombocytopenia, usually defined as a platelet count below 50 000/μl, although the incidence is higher when patients with AIDS are not included. Patients with an initial platelet count <100 000/μl appear to be at increased risk of developing thrombocytopenia.[1]

Less common haematological adverse effects during ganciclovir therapy include anaemia (estimated incidence 2%) and eosinophilia. Leucopenia has also been reported but is usually mild and may reflect reduced numbers of specific cell populations (neutrophils for example).[1]

All haematological adverse events attributable to ganciclovir appear to be readily reversible upon withdrawal of the drug, although cases of intractable neutropenia and thrombocytopenia, some fatal, have been reported.[1,181]

4.1.2 Use of Haematopoietic Growth Factors to Prevent Ganciclovir-Associated Neutropenia

Haematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage CSF (GM-CSF) stimulate the growth and development of immature progenitor cells to form colonies of mature cells[184] and have been evaluated as a countermeasure to ganciclovir-induced neutropenia. Data are limited here and have almost invariably been generated in small groups of patients with AIDS-related cytomegalovirus infection, although a case series in liver transplant recipients is also available.

Jacobson et al.[185] administered recombinant G-CSF to 7 patients with AIDS-related cytomegalovirus infection unable to tolerate ganciclovir because of neutropenia. Intermittent subcutaneous injections of recombinant G-CSF 300 μg/dose were administered with the aim of achieving a nadir neutrophil count of 500 to 1500/μl. Six patients restarted ganciclovir at a dosage of 5 mg/kg once or twice daily while the seventh received the drug at a dosage of 6 mg/kg/day 5 days/week. All patients tolerated ganciclovir therapy when G-CSF was given concurrently. Similarly, Diflo et al.[186] found that G-CSF enabled reinstitution of ganciclovir therapy in 3 liver transplant recipients with cytomegalovirus infection who developed intolerable neutropenia during ganciclovir monotherapy.

Preliminary results from an ongoing randomised double-blind trial comparing ganciclovir monotherapy (5 mg/kg intravenously every 12 hours for 14 days and 5 mg/kg/day thereafter) with the same ganciclovir regimen combined with recombinant GM-CSF (1 to 8 μg/kg/day titrated to achieve and maintain an absolute count of 2500 to 5000 neutrophils/μl) in patients with AIDS-related cytomegalovirus retinitis have been published.[187] A neutrophil count <750 cells/μl occurred in 12 of 21 (57%) ganciclovir monotherapy recipients versus 6 of 15 (40%) ganciclovir plus recombinant GM-CSF recipients. 68 versus 20 neutropenic episodes were recorded.[187]

4.2 Other Adverse Effects

Central nervous system adverse events, including confusion, seizures, abnormal thought patterns, psychosis, hallucinations, changes in mental status, nightmares, anxiety, tremor, dysesthesia, ataxia, coma, headache and somnolence, have been reported in about 5% of ganciclovir recipients.[1,70,117,181,188-195]

Abnormal liver function values, fever and rash have each been reported in approximately 2% of ganciclovir recipients.[1] Events reported in ≤1% of patients include chills, oedema, infection, malaise, arrhythmia, alterations in blood pressure, nausea, vomiting, anorexia, diarrhoea, dyspnoea, reduced blood glucose levels, alopecia, reduced kidney function and inflammation, pain or phlebitis at the infusion site.[1]

Intraocular injection of ganciclovir has been associated with transient increases in intraocular pressure, coupled with intense pain lasting approximately 30 minutes, and total amaurosis (resultant from total interruption of retinal blood flow) lasting for between 1 and 10 minutes after injection.[196] One case of *Xanthomonas maltophilia* endophthalmitis has been reported in a patient with AIDS-related cytomegalovirus retinitis treated

with an intraocular sustained-release preparation of ganciclovir.[197]

4.3 Tolerability in Combination with Antiretroviral Drugs

Patients with AIDS who require ganciclovir therapy are likely to be receiving, or will eventually require, antiretroviral therapy. The primary concern when ganciclovir and zidovudine are administered concomitantly is additive haematological toxicity.

The apparent lack of haematological toxicity in patients treated with the zidovudine congener didanosine[198] suggests that combined treatment with ganciclovir and this agent may be better tolerated than combined treatment with ganciclovir and zidovudine. Results from a retrospective analysis revealed dose-limiting neutropenia (<500 cells/μl) occurred in 3 of 32 (9.4%) patients with AIDS-related cytomegalovirus disease treated with ganciclovir and didanosine. The absolute neutrophil count fell to between 500 and 749 cells/μl in a further 9 (28.1%) patients, and 6 (18.8%) patients received red blood cell transfusions.[199]

5. Drug Interactions

The toxicity profiles of ganciclovir and zidovudine overlap; thus, additive toxicity may necessitate a reduction in zidovudine dosage when the 2 drugs are given together.

There have been several reports of seizures in patients receiving the antibacterial drug imipenem/cilastatin and ganciclovir concomitantly. Caution is thus recommended if these drugs are to be used together.[1,181]

The use of ganciclovir in conjunction with other drugs that inhibit the replication of bone marrow, spermatogonia, and cutaneous and gastrointestinal germinal layers, including dapsone, pentamidine, flucytosine, vincristine, doxorubicin, amphotericin B and trimethoprim/sulpha drug combinations, is not recommended unless potential beneficial effects outweigh the associated risk.[1]

Drugs such as probenecid that inhibit renal tubular secretion or resorption may reduce clearance of ganciclovir and thus increase plasma concentrations of the drug.[1]

6. Dosage and Administration

The recommended induction dosage regimen for ganciclovir as treatment for patients with cytomegalovirus retinitis and normal renal function is 5 mg/kg (as a constant intravenous infusion over 1 hour) every 12 hours for 14 to 21 days. If required, maintenance doses of 5 mg/kg/day (as a constant intravenous infusion over 1 hour) 7 days/week, or 6 mg/kg/day (similarly administered) 5 days/week, can be given following the initial induction regimen; patients who relapse during maintenance therapy can be given a second course of induction therapy. The same dosages, but a shorter (7 to 14 days) induction regimen, are recommended for the prevention of cytomegalovirus disease in transplant recipients.

The drug should be infused over a 1-hour period, since rapid or bolus injection may produce excessive plasma ganciclovir concentrations and thus predispose the patient to adverse events. The alkaline pH (approximately 11) of ganciclovir in solution may cause severe tissue irritation when the drug is administered subcutaneously or intramuscularly and these administration routes are not recommended.

The following dosage regimens are recommended for patients with renal impairment:

- Creatinine clearance ≥4.8 L/h/1.73m^2 (≥80 ml/min/1.73m^2) – 5 mg/kg every 12 hours
- Creatinine clearance 3 to 4.75 L/h/1.73m^2 (50 to 79 ml/min/1.73m^2) – 2.5 mg/kg every 12 hours
- Creatinine clearance 1.5 to 2.95 L/h/1.73m^2 (25 to 49 ml/min/1.73m^2) – 2.5 mg/kg every 24 hours
- Creatinine clearance <1.5 L/h/1.73m^2 (<25 ml/min/1.73m^2) – 1.25 mg/kg every 24 hours.

The drug is effectively cleared in patients undergoing haemodialysis.[1] Renal function should generally be monitored at least once every 2 weeks in patients receiving ganciclovir. Haematological parameters should be closely monitored during

treatment; a neutrophil count of <500/μl or a platelet count <25 000/μl indicate that ganciclovir therapy should be withdrawn. Ganciclovir should not be restarted until evidence of marrow recovery is observed (absolute neutrophil count >750/μl).

Intravitreal ganciclovir is generally given at a dose of 200 to 400μg once or twice weekly during induction therapy, then weekly during maintenance therapy.

The safety of ganciclovir in children has not been established and extreme caution is warranted before the drug is used in this population because of the probability of long term carcinogenicity and reproductive toxicity. Indeed, ganciclovir should only be given to children when the potential benefits of treatment outweigh the risks.[200]

7. Place of Ganciclovir in Therapy

The publication of much information since the previous review in *Drugs*[1] has more clearly defined the role of ganciclovir in the treatment of cytomegalovirus infection in patients with AIDS and in transplant recipients. However, trials have almost invariably had limited controls for variation and bias and involved small groups of patients, especially those conducted in patients with AIDS. Nevertheless, most have shown treatment with ganciclovir to be beneficial. Although AIDS-related cytomegalovirus retinitis responds to induction therapy with intravenous ganciclovir in approximately 80% of patients, complete regression cannot be achieved and indefinite maintenance therapy is required to prevent progression. Limited data suggest that AIDS-related cytomegalovirus infection refractory to ganciclovir monotherapy may respond to ganciclovir in combination with cytomegalovirus immune globulin or foscarnet.

There has been considerable interest regarding the comparative efficacy of ganciclovir and foscarnet, the only other drug currently available for the treatment of cytomegalovirus retinitis. Although few direct comparisons have been conducted, it appears that the 2 drugs are similar in terms of therapeutic efficacy; however, the largest study to compare ganciclovir and foscarnet, the SOCA and ACTG trial,[98] showed a lower mortality rate in foscarnet versus ganciclovir recipients (34% *vs* 51%; p = 0.007). AIDS is a terminal condition and any intervention shown to prolong survival in patients with AIDS must be viewed as beneficial. Thus, considerable emphasis has been placed on the survival results of the SOCA and ACTG trial. Although this is an important result, more foscarnet recipients switched to ganciclovir because of toxicity than vice versa and considerably fewer ganciclovir than foscarnet recipients received full doses of zidovudine. Further studies are required in this area before definitive conclusions can be drawn. In particular, studies comparing ganciclovir and foscarnet incorporating the use of G-CSF or GM-CSF to prevent ganciclovir-associated neutropenia – thus enabling the use of full therapeutic doses of zidovudine – are required. Additionally, since infusion of ganciclovir appears to be less time consuming than infusion of foscarnet,[201] studies designed to quantify quality of life issues are required.

Adverse events during systemic ganciclovir maintenance therapy, notably neutropenia, often necessitate withdrawal of the drug. In addition, concurrent administration of systemic ganciclovir and zidovudine often produces additive haematological toxicity necessitating withdrawal of 1 or both drugs. Since retinitis invariably progresses in the absence of treatment, alternative methods for giving the drug have been examined with the aim of improving tolerability. Intraocular administration of ganciclovir avoids systemic adverse effects and has produced response rates comparable to those obtained during intravenous therapy in patients with AIDS-related cytomegalovirus retinitis. The unpleasant nature of intravitreal injection has prompted the development of controlled-release formulations intended to reduce the number of intraocular injections required. Results from preliminary studies investigating the therapeutic use of these formulations have been promising as have those from studies evaluating the efficacy of orally administered ganciclovir.

Peripheral retinitis has been shown to progress rapidly when antiviral therapy is deferred.[80,202] Thus, delayed commencement of ganciclovir therapy in patients with AIDS-related retinitis that is not immediately sight-threatening does not appear to be feasible.

Ganciclovir has also shown efficacy in other types of cytomegalovirus infection. Favourable results from noncomparative trials evaluating the use of ganciclovir in patients with AIDS-related gastrointestinal cytomegalovirus infection have been supported by those from a double-blind trial which showed ganciclovir to be significantly more effective than placebo.

Cytomegalovirus infection is often problematic in transplant recipients. The use of ganciclovir as prophylaxis or as early treatment appears to be most beneficial in bone marrow transplant recipients; treatment of established cytomegalovirus infection with ganciclovir in these patients has generally been unsuccessful. On the other hand, treatment for established cytomegalovirus infection does appear to be effective in solid organ transplant recipients.

Limited data regarding the use of ganciclovir in paediatric transplant recipients have shown the drug to be effective as prophylaxis against, and treatment for, cytomegalovirus infection in children who had undergone liver transplantation. One study in paediatric renal transplant recipients has shown ganciclovir to be more effective when administered prophylactically than as treatment for established cytomegalovirus infection.

Ganciclovir has been used to treat a number of neonates/infants with congenital cytomegalovirus infection. Outcome was generally poor but appeared to be more favourable in infants treated for longer periods of time. Larger trials are needed to evaluate the efficacy and safety of extended treatment with ganciclovir in this difficult indication.

In conclusion, while further direct comparisons with foscarnet which include assessment of survival in patients with AIDS, ideally incorporating the use of G-CSF or GM-CSF to prevent ganciclovir-associated neutropenia, are necessary, ganciclovir has established a valuable role in the treatment of cytomegalovirus infection in patients with AIDS and in organ transplant recipients. Ganciclovir also seems likely to find a place as prophylaxis or early treatment of asymptomatic infection in bone marrow transplant recipients.

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Erratum

Vol. 47, No. 5, 1994, page 838: The third sentence in the first paragraph of section 3.1 Bacteraemia and Endocarditis should read, 'In 12 patients with endocarditis caused by *S. aureus* or mycotic aneurism. . . .'.

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