Drugs 39 (4): 597-638, 1990
0012-6667/90/0004-0597/$21.00/0

DREND2 106

Ganciclovir
A Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy in Cytomegalovirus Infections

Diana Faulds and *Rennie C. Heel*

ADIS Drug Information Services, Auckland, New Zealand

Various sections of the manuscript reviewed by: ***C.S. Crumpacker,*** Department of Medicine, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts, USA; ***E. De Clercq,*** Rega Instituut, Katholieke Universiteit, Leuven, Belgium; ***B. de Hemptinne,*** Departement De Chirurgie, Universite Catholique De Lourain Cliniques Universitaires Saint-Luc, Bruxelles, Belgium; ***J. Harmenberg,*** Department of Virology, National Bacteriological Laboratory, Stockholm, Sweden; ***M.E. Heath-Chiozzi,*** Department of Medicine, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts, USA; ***W.G. Ho,*** Department of Medicine, UCLA Medical Center, Los Angeles, California, USA; ***D.J. Jeffries,*** Department of Medical Microbiology, Wright Fleming Institute, St Mary's Hospital Medical School, London, England; ***O.L. Laskin,*** Department of Medicine and Pharmacology, Cornell University Medical College, New York, New York, USA; ***T. Naito,*** Department of Ophthalmology, Tokushima University School of Medicine, Tokushima, Japan; ***R.F. Schinazi,*** Veterans Administration Medical Center, Decatur, Georgia, USA; ***J-P. Sommadossi,*** Division of Clinical Pharmacology, The University of Alabama at Birmingham, Birmingham, Alabama, USA.

Contents

Summary 598
1. Antiviral Activity 600
  1.1 Antiviral Activity *In Vitro* 600
    1.1.1 Human Cytomegalovirus 601
    1.1.2 Herpes Simplex Virus Types 1 and 2 601
    1.1.3 Other Human DNA Viruses 603
    1.1.4 Activity in Combination With Other Antiviral Agents 603
  1.2 Antiviral Activity *In Vivo* 607
    1.2.1 Cytomegalovirus Infections 607
    1.2.2 Herpes Simplex Virus Types 1 and 2 608
  1.3 Mechanism of Action 609
  1.4 Viral Resistance to Ganciclovir 612
2. Toxicology Studies 612
3. Pharmacokinetic Studies 613
  3.1 Absorption and Plasma Concentrations 613
    3.1.1 Intravenous Administration 613
    3.1.2 Intraocular and Oral Administration 614
  3.2 Distribution 614
  3.3 Metabolism and Elimination 615
  3.4 Pharmacokinetics in Patients with Renal Function Impairment 615
4. Therapeutic Use in Cytomegalovirus Infections 616

4.1 Cytomegalovirus Retinitis 617
4.1.1 Intravenous Ganciclovir Therapy 618
4.1.2 Intravitreal Ganciclovir Therapy 619
4.2 Cytomegalovirus Pneumonia 623
4.2.1 Ganciclovir Monotherapy 623
4.2.2 Combination Therapy with Ganciclovir and Cytomegalovirus Immune Globulin 625
4.3 Cytomegalovirus Gastrointestinal Disease and Hepatitis 626
4.4 CNS and Disseminated Cytomegalovirus Infection 626
4.5 Prophylactic Ganciclovir Therapy 627
5. Adverse Effects 627
5.1 Haematological Effects 627
5.2 Other Adverse Effects 630
6. Drug Interactions 631
7. Dosage and Administration 631
8. Place of Ganciclovir in Therapy 632

Summary

Synopsis

Ganciclovir is a nucleoside analogue with antiviral activity in vitro *against members of the herpes group and some other DNA viruses. It has demonstrated efficacy against human cytomegalovirus infections and should be considered a first-line therapy in the treatment of life- or sight-threatening cytomegalovirus infection in immunocompromised patients. Clinical efficacy varies with the underlying aetiology of immunocompromise and the site of disease, and prompt diagnosis and early treatment initiation appear to improve the response. In patients with cytomegalovirus pneumonia, particularly bone marrow transplant recipients, concomitant administration of cytomegalovirus immune globulin may significantly improve clinical outcome. Maintenance therapy to prevent recurrence is usually required by bone marrow transplant recipients until the recovery of adequate immune function, whereas AIDS patients may require indefinite ganciclovir maintenance therapy to prevent disease progression, as ganciclovir (like other antivirals) does not eradicate latent viral infection. Haematological effects occur relatively frequently during ganciclovir administration but are usually reversible. Ganciclovir has not been directly compared with other antiviral drugs because of the absence until recently of other effective treatments. However, comparative studies with foscarnet, particularly in cytomegalovirus retinitis, will be of considerable interest.*

Thus, ganciclovir represents a major advance in the therapy of severe cytomegalovirus infections in immunocompromised patients. Comparative studies, and investigation of ways of reducing toxicity (intravitreal administration; concomitant use of stimulants of haematopoiesis; use in conjunction with other antivirals with differing mechansisms of action), may further expand its eventual role.

Antiviral Activity

Ganciclovir exhibits *in vitro* activity against human cytomegalovirus and herpes simplex virus types 1 and 2, and to a lesser degree, Epstein-Barr virus, varicella zoster virus, human herpesvirus 6 and human adenoviruses. Although results vary depending on the viral strain and methodological considerations, in general ganciclovir is considerably more potent than aciclovir (acyclovir) against cytomegalovirus and tends to be more potent against herpes simplex viruses. Studies of its activity against other viruses and comparisons with other antiviral agents are limited, but ganciclovir is more active than many other nucleoside analogues against cytomegalovirus, and appears to inhibit the productive cycle but not the latent phase of Epstein-Barr virus in a manner similar to aciclovir. Synergism of ganciclovir with interferons against human cytomegalovirus and with fos-

carnet and interferons against herpes simplex viruses has been demonstrated in various *in vitro* assays. The mechanism of action of ganciclovir involves highly selective inhibition of viral DNA replication as a result of enhanced uptake by infected cells, phosphorylation by viral thymidine kinase and/or cellular kinase enzymes, and substrate specificity for viral rather than cellular DNA polymerases.

Although an *in vivo* animal model of human cytomegalovirus infection has not been developed, studies of cytomegalovirus infections in animals have demonstrated the antiviral efficacy of ganciclovir and indicate greater potency than aciclovir in pulmonary infections. The beneficial effects of concomitant ganciclovir and cytomegalovirus antiserum have also been demonstrated in encephalitis and disseminated infection in animal studies. Models of pulmonary cytomegalovirus infection indicate that ganciclovir reduces viral titres but not interstitial pneumonitis. Limited data from animal studies suggest prophylactic ganciclovir may prevent cytomegalovirus infection. Ganciclovir was also effective in *in vivo* models of various herpes simplex virus type 1 and 2 infections. However, like aciclovir, ganciclovir was unable to eradicate established latent herpesvirus infection.

Mutations in the viral DNA polymerase gene and/or the viral genes involved in ganciclovir monophosphorylation appear to mediate the development of ganciclovir resistance in cytomegalovirus and herpes simplex virus infections, and may also confer cross-resistance to other antiviral agents. The incidence and clinical significance of viral resistance to ganciclovir remains to be fully determined.

Pharmacokinetics

Following intravenous administration, peak ganciclovir concentrations in plasma vary in a linear fashion over the therapeutic dose range. With an 8-hourly dosage regimen, steady-state plasma concentrations of about 9 to 45 μmol/L are observed over a dose range of 1 to 5 mg/kg and are similar to those seen after equivalent single doses. Furthermore, no evidence of ganciclovir accumulation has been observed in patients with normal renal function. Intravitreal ganciclovir administration produces high concentrations in intravitreal fluid, apparently with minimal systemic absorption. The low bioavailability of oral ganciclovir may preclude the use of this administration route.

Ganciclovir concentrations in CSF were 31 to 67% of plasma concentrations reported following intravenous administration, while subretinal fluid concentrations several hours after an infusion of ganciclovir 5 mg/kg were similar to or exceeded plasma concentrations. Ganciclovir is only minimally bound to plasma proteins (1 to 2%). The volume of distribution at steady-state is about 33 to 45L. In patients with normal renal function almost 100% of an intravenous ganciclovir dose is excreted in the urine with an elimination half-life of 2 to 4 hours. Ganciclovir clearance decreases linearly with decreasing creatinine clearance, with elimination half-life increasing to 30 to 40 hours in severe renal dysfunction; however, plasma ganciclovir concentrations are significantly reduced by haemodialysis. The half-life of ganciclovir in vitreous fluid following intravitreal administration is about 13 hours.

Therapeutic Use

Ganciclovir has been almost exclusively evaluated in immunocompromised patients with cytomegalovirus infections, including retinitis, pneumonia, gastrointestinal, hepatic, CNS and disseminated infections. Many patients have been treated under 'compassionate plea' protocols, mainly because patients requiring ganciclovir therapy usually have life- or sight-threatening cytomegalovirus disease. Placebo-controlled and comparative studies are reportedly underway. Ganciclovir has generally proved effective, although the degree of response varies according to disease site and the underlying aetiology of immunocompromise, and efficacy is not well established in some indications (CNS infections). Patients with cytomegalovirus pneumonia, particularly bone marrow transplant recipients, may develop fatal interstitial pneumonitis despite apparent virological cure, and concomitant cytomegalovirus immune globulin administration appears to considerably increase the likelihood of a favourable therapeutic outcome in these patients. Prompt diagnosis and early institution of ganciclovir therapy also appear to improve the response to therapy.

Maintenance ganciclovir therapy is usually required by patients with acquired immune deficiency syndrome (AIDS) and bone marrow transplant recipients to prevent cytomegalovirus disease relapse since, as with other antiviral drugs, ganciclovir does not eradicate latent viral infections. However, ganciclovir therapy may usually be withdrawn in the latter group of patients as immune function recovers. Ganciclovir has been successfully used in a small number of children and in the elderly. Intravitreal ganciclovir therapy appears effective in those AIDS patients with cytomegalovirus retinitis in whom intravenous ganciclovir is likely to cause unacceptable toxicity (for example, patients receiving zidovudine). However, it is not a substitute for systemic therapy as it is not effective against the disseminated cytomegaloviral disease which is usually found in association with cytomegalovirus retinitis.

Adverse Effects

Adverse effects requiring interruption or withdrawal of ganciclovir therapy occur in about 32% of patients, although subsequent reintroduction of ganciclovir or use of a reduced dosage regimen is often successful. Haematological changes are the most commonly observed unwanted effects, particularly neutropenia (about 40% of patients) and thrombocytopenia (about 20%), although these are usually reversible. Patients with AIDS may be particularly susceptible to developing neutropenia during ganciclovir therapy. Concomitant administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) may serve to moderate the depressive effects of ganciclovir on granulocyte production. Inhibition of spermatogenesis and fertility has been observed in animal models at ganciclovir doses lower than those recommended in humans, but this effect has not been observed clinically. A variety of other adverse effects have been reported, although their association with ganciclovir is often unclear as the underlying cause of immunocompromise and concomitant medications and infections may be involved.

Drug Interactions

Ganciclovir and zidovudine have overlapping toxicity profiles, and in general the use of ganciclovir concurrently with drugs that inhibit the replication of rapidly dividing cell populations or alter renal function should be approached with caution. In addition, seizures may be associated with the concomitant use of ganciclovir and imipenem/cilastatin.

Dosage and Administration

Currently, ganciclovir is recommended for use only in immunocompromised patients with life- or sight-threatening cytomegalovirus disease. In patients with normal renal function ganciclovir should be administered as a 1-hour intravenous infusion at a dosage of 2.5 mg/kg 8-hourly or 5 mg/kg 12-hourly for 14 to 21 days. Maintenance therapy to prevent recurrences is usually required in patients with AIDS or in bone marrow transplant recipients. A maintenance regimen of 5 mg/kg/day, or 6 mg/kg/day 5 days/week is recommended, with patients experiencing progressive cytomegalovirus disease during maintenance being retreated with the induction regimen. Ganciclovir dosage should be reduced in patients with impaired renal function (table X, section 7).

1. Antiviral Activity

Ganciclovir, an acyclic analogue of the natural nucleoside 2′-deoxyguanosine (fig. 1), selectively inhibits replication of members of the *Herpesviridae* family and also exhibits some activity against other DNA viruses. The antiviral activity of this aciclovir (acyclovir) congener has been evaluated *in vitro* and in animal models. Aspects of the mechanism of action of ganciclovir, possible synergism of ganciclovir in combination with other antiviral agents, immunoglobins and interferons, and the mechanism of viral resistance to ganciclovir have been evaluated in more recent studies.

1.1 Antiviral Activity *In Vitro*

The *in vitro* antiviral activity of ganciclovir against human cytomegalovirus and herpes simplex virus has been extensively evaluated. *In vitro*

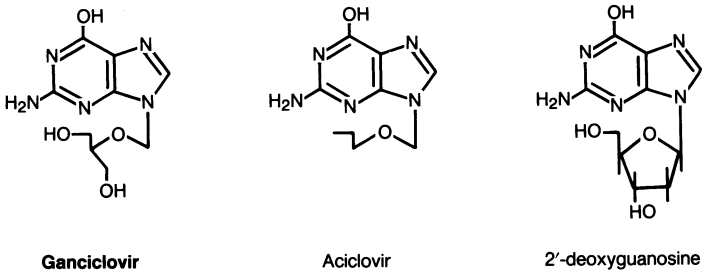

Fig. 1. Chemical structure of the acyclic nucleosides ganciclovir and aciclovir, and their purine nucleoside analogue 2′-deoxyguanosine. Synonyms for ganciclovir include 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl} guanine, 9-(1,3-dihydroxy-2-propoxymethyl)guanine, BW 759U, DHPG, 2′NDG, BIOLF-62.

studies have also indicated that ganciclovir has some activity against varicella zoster virus and Epstein-Barr virus infections and some studies have found useful activity against human adenoviruses and human herpesvirus 6. *In vitro* susceptibility testing is an important method of determining the antiviral spectrum of activity of a potential therapeutic agent initially, but information obtained from *in vitro* studies does not always correlate with clinical efficacy. The therapeutic ratio of a potential agent is of considerably greater clinical relevance than 50% viral inhibition results as it provides a better indication of the potential *in vivo* usefulness of the drug. Furthermore, marked variation in the susceptibility of viruses to ganciclovir (and other antiviral agents) may be observed according to the virus strain, host cell type and assay method used (see tables I, II & III), and as yet the method for determining *in vitro* susceptibility to ganciclovir does not appear to have been standardised. The host immune response is also an important variable that is absent in *in vitro* susceptibility testing (Fraser-Smith et al. 1984a; Pulliam et al. 1986). However, *in vitro* testing does provide an initial guide to possible *in vivo* efficacy.

1.1.1 Human Cytomegalovirus

As an illustration of the difficulty and variability of *in vitro* study of antiviral activity, an early study using human cytomegalovirus immediate early antigen expression as a measure of antiviral activity failed to show any significant ganciclovir activity (Smith et al. 1982a). However, subsequent studies confirmed the activity of ganciclovir against human cytomegalovirus *in vitro* (table I), and revealed that infectious virus production and DNA synthesis were markedly reduced at low ganciclovir concentrations. The effects on viral protein synthesis (and therefore early antigen expression) were minimal in comparison at these concentrations (section 1.3; Mar et al. 1983; Rasmussen et al. 1984).

Most studies reported ganciclovir concentrations of 0.5 to 3.0 μmol/L as achieving 50% inhibition (ID_{50}) of viral plaque formation, DNA synthesis or yield (table I). This is in contrast to aciclovir, which has proved relatively inactive *in vitro* against human cytomegalovirus with ID_{50} values from around 10 μmol/L to more than 200 μmol/L (Gadler 1983). As previously reviewed in the Journal (O'Brien & Campoli-Richards 1989; Richards et al. 1983) and reported by Gadler (1983), ganciclovir appears to be more potent *in vitro* than vidarabine, foscarnet, idoxuridine and trifluridine against human cytomegalovirus.

1.1.2 Herpes Simplex Virus Types 1 and 2

Herpes simplex virus type 1 strains appear to be more susceptible to ganciclovir *in vitro* than type 2 strains, although there is a considerable overlap in the range of reported concentrations achieving 50% inhibition (ID_{50}) of viral plaque formation or virus-induced cytopathogenicity (table II). In most studies ganciclovir 0.2 to 2.0 μmol/L for herpes simplex virus type 1 strains and 0.3 to 10 μmol/L

Table I. Summary of the *in vitro* activity of ganciclovir and aciclovir against human cytomegalovirus (HCMV)

Reference	Cell culture[a]	Viral assay method	Virus (strain)	Concentration achieving 50% inhibition[b] (μmol/L)	
				ganciclovir	aciclovir
Biron et al. (1985)	MRC-5, HFF	Plaque reduction	HCMV (AD169)	1.7	108
			HCMV (Wade)	0.8	54
Biron et al. (1986)	HFF	Plaque reduction	HCMV (AD169)	1	190
Cheng et al. (1983b)	WI-38	Plaque reduction	HCMV	1.0-4.8	75-98
Cole & Balfour (1987)	HFF	Plaque reduction	HCMV (AD169)	3.1	60.5
			HCMV	0.94-6.31	20.7-126.2
Dankner & Spector (1988)		DNA hybridisation	HCMV	2.9	
Duke et al. (1986)	MRC-5	Plaque reduction	HCMV (AD169)	4.5	
			HCMV (Davis)	4.9	
Field et al. (1983)	MRC-5	Plaque reduction	HCMV (AD169)	1.6-6.3	110
			HCMV (Towne)	0.4-2.4	10-80
Freitas et al. (1985)	MRC-5, HET	Plaque reduction	HCMV (AD169)	7, 7	95, 55
			HCMV (Davis)	7, 5	64, 39
Mar et al. (1983)	WI-38	Plaque reduction	HCMV	1.0-4.8	
Plotkin et al. (1985)	HEL	Plaque reduction	HCMV (AD169)	1-2	
			HCMV	0.4-11	
Rasmussen et al. (1984)	HEL	Yield reduction	HCMV	0.01-1.0	
Rush & Mills (1987)	HFF	Plaque reduction	HCMV (AD169)	0.43	100
			HCMV	0.08-0.6	60-≥100
Smee et al. (1983b)	MRC-5	Plaque reduction	HCMV (AD169)	7	95
Smith et al. (1982a)	HEF	Antigen expression	HCMV (AD169)	>400	
Taylor et al. (1988)	HEF	Plaque reduction	HCMV (Towne)	0.5-1.2	
			HCMV (Kerr)	0.6	
Tocci et al. (1984)	MRC-5, HEL	Plaque reduction	HCMV	0.94-5.9	36-135
Tolman et al. (1985)	MRC-5	Plaque reduction	HCMV (AD169)	3	10
Tyms et al. (1984)	HEF	Plaque reduction	HCMV	0.55-3.9	20-91

a MRC-5, HEL = human embryo lung cells; HFF = human foreskin fibroblasts; WI-38 = human fibroblasts; HET = human embryo tonsil cells; HEF = human embryo fibroblasts.

b Results reported in mg/L were converted to μmol/L. Results were reported as ID_{50} or ED_{50} values = drug concentration inhibiting viral plaques, DNA synthesis, antigen expression or virus-induced cytopathogenicity by 50%.

for type 2 strains has achieved 50% viral inhibition.

Ganciclovir tends to be more potent *in vitro* than aciclovir against herpes simplex virus types 1 and 2, and is more potent than foscarnet or vidarabine against type 1 (table II); it is also more potent than phosphonoacetic acid (PAA), aphidicolin, idoxuridine and trifluridine against type 1 strains (Larder & Darby 1986). Limited comparative data suggest bromovinyl deoxyuridine (BVDU) is more potent than ganciclovir against type 1 strains but less potent against type 2 strains. The potency of 2′-fluoro-5-iodoarabinosylcytosine (FIAC) and 2′-fluoro-2′-deoxy-5-methyl-arabinofuranosyluracil (FMAU) *in vitro* was similar to that of ganciclovir but both agents exhibited cytotoxicity at relatively low concentrations (Smee et al. 1985b). *In vitro* reactivation of latent herpes simplex virus type 1 in trigeminal ganglia was prevented by ganciclovir 32 mg/L (126 μmol/L) and reduced by 50% by 0.125 (0.5 μmol/L) and 0.5 mg/L (2.0 μmol/L) [Klein & Friedman-Kien 1985].

1.1.3 Other Human DNA Viruses

A few studies also investigated the *in vitro* antiviral activity of ganciclovir against varicella zoster virus, Epstein-Barr virus, human herpesvirus 6 and human adenovirus infections (table III). Ganciclovir achieves 50% inhibition of varicella zoster virus at concentrations similar to, or slightly higher than, those required for aciclovir or vidarabine, while limited data suggest BVDU and FIAC are considerably more potent and foscarnet has similar or slightly reduced potency compared with ganciclovir (O'Brien & Campoli-Richards 1989).

Ganciclovir showed considerably greater potency against Epstein-Barr virus than did aciclovir, inhibiting the transformation of human cord lymphocytes to lymphoblastoid phenotype and inhibiting genome replication in P3HR-1 cells and superinfected Raji cells at concentrations of 0.05 to 20 μmol/L (table III; Lin et al. 1984; van der Horst et al. 1987). However, antigen expression was not significantly affected at these concentrations and replication of episomal Epstein-Barr virus, which does not require a virus-encoded DNA polymerase, was not inhibited in latently infected Raji cells by either drug (Lin et al. 1984; van der Horst et al. 1987). The effects of ganciclovir on active Epstein-Barr virus replication were prolonged compared with the effects of aciclovir, persisting for 21 days compared with 11 days following removal of the drug (Lin et al. 1984). Results from 1 study suggested FIAC and FMAU had a greater activity against Epstein-Barr virus than ganciclovir *in vitro*, but also exhibited considerably greater cytotoxicity (Lin et al. 1985).

Human adenoviruses are another group of DNA viruses that have shown limited *in vitro* susceptibility to ganciclovir. Although ID_{50} values for the different adenovirus serotypes were up to 40-fold greater than those reported for human cytomegalovirus *in vitro*, for those adenoviruses in subgenus D the ID_{50} values were similar to those reported for human cytomegalovirus whereas other genotypes appeared less susceptible (Taylor et al. 1988).

1.1.4 Activity in Combination With Other Antiviral Agents

Combination therapy with agents exhibiting synergistic antiviral effects offers several potential advantages, including enhanced activity against the pathogen at drug concentrations that are better tolerated and more easily achieved *in vivo*, and reduced frequency of emergence of resistant strains, particularly when drugs with differing modes of action are utilised (Moran et al. 1985; Smith et al. 1982b). *In vitro* studies evaluating the potential synergistic effects of ganciclovir in combination with other antiviral agents are limited and methods evaluating the nature of the interaction (that is, synergistic, additive or antagonistic) remain to be standardised. However, several drug combinations have demonstrated potentially useful results.

Human Cytomegalovirus

Combinations of ganciclovir and other antiviral agents have synergistic antiviral effects against human cytomegalovirus *in vitro*. In human embryo lung cells ganciclovir 0.01 μmol/L, 0.1 μmol/L or 1.0 μmol/L acted synergistically with recombinant human interferon-β 10U or 30U against human cytomegalovirus (AD169) in plaque reduction assays, with synergism being dose-proportional in this concentration range. Ganciclovir also acted synergistically in combination with recombinant human interferon-β ser-17 10U at these concentrations but other dosage combinations exhibited additive effects. In combination with ganciclovir, recombinant human interferon-α or recombinant human interferon-α D showed only additive antiviral effects (Rasmussen et al. 1984). In human foreskin fibroblasts ganciclovir 0.025 μmol/L, 0.25 μmol/L or 2.5 μmol/L exhibited synergistic antiviral effects in combination with the polyamine synthesis inhibitor α-difluoromethylornithine (DFMO) 5 mmol/L or 22 mmol/L against 5 clinical human cytomegalovirus isolates, particularly when assayed by yield reduction. The effects of DFMO alone on human cytomegalovirus were inconsistent in this study (Rush & Mills 1987), but this agent shows low toxicity in humans and may be clinically useful in combination with ganciclovir. DNA

Table II. Summary of the *in vitro* activity of ganciclovir, aciclovir, vidarabine, bromovinyldeoxyuridine (BVDU), foscarnet and 2′-fluoro-5-iodoarabinosylcytosine (FIAC) against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2)

Reference	Cell culture[a]	Viral assay method	Virus (strain)	Concentration achieving 50% inhibition[b] (μmol/L)					
				ganciclovir	aciclovir	vidarabine	BVDU	foscarnet	FIAC
Activity against herpes simplex virus type 1 (HSV-1)									
Ashton et al. (1982); Field et al. (1983)	PRK	Cytopathogenicity	HSV-1 (Schooler)	3.9-11.8[c]	4.5-13	230-450	0.3-0.7	230	2.3-4.5
		Plaque reduction	HSV-1 (Schooler)	0.98	1.1				
Coen et al. (1985)	Vero	Plaque reduction	HSV-1 (KOS)	0.5-1.5					
Collins & Oliver (1985)	Vero H	Plaque reduction	HSV-1	0.57	1.34				
			HSV-1	0.24-1.33	0.35-1.44				
	Multiple[d]		HSV-1 (ICI)	0.0005-1.04	0.01-2.05				
Larder & Darby (1986)	BU-BHK	Plaque reduction	HSV-1 (SC16)	0.17	0.15	6.7	0.02	26	
McLaren et al. (1985)	Vero	Cytopathogenicity	HSV-1	1.0-8.0	4.6-7.0		0.7-7.0	110-220	1.67-4.5
Moran et al. (1985)	HFF	Cytopathogenicity	HSV-1 (E-377)	0.27		48			
Pulliam et al. (1986)	Vero	Plaque reduction	HSV-1 (KOS)	2.2	2.7	90	0.7		
			HSV-1 (H129)	0.63	0.9	39	0.7		
Smee et al. (1983, 1985b)	Vero	Plaque reduction	HSV-1	0.2-0.5	0.5-1.0				0.3-0.5
Smith et al. (1982a,b)	HEF	Plaque reduction	HSV-1 (Patton)	0.34-0.98	3.0				
	Multiple[d]			0.4-1.2					
St Clair et al. (1984)	Vero	Plaque reduction	HSV-1 (KOS)	0.2	0.7				
			HSV-1 (Patton)	0.7	1.4				
Tocci et al. (1984)	MRC-5	Plaque reduction	HSV-1 (Schooler)	0.4-0.8	1.8				
Tolman et al. (1985)	MRC-5	Plaque reduction	HSV-1 (Schooler)	1	1-2				
van der Horst et al. (1987)	P3HR-1	Plaque reduction	HSV-1	1.5	3.5				
Activity against herpes simplex virus type 2 (HSV-2)									
Ashton et al. (1982); Field et al. (1983)	PRK	Cytopathogenicity	HSV-2 (Curtis)	3.9-11.8	4.5-13	450	27-230	450	2.3-4.5
Coen et al. (1985)	Vero	Plaque reduction	HSV-2 (HG52)	3.2					
Collins & Oliver (1985)	Vero H	Plaque reduction	HSV-2	1.67	1.78				

Moran et al. (1985)	HFF	Cytopathogenicity	HSV-2 (MS)	1.2	21	
Smee et al. (1983, 1985b)	Vero	Plaque reduction	HSV-2	0.3-1.8	0.5-2.4	0.9-1.3
Smith et al. (1982a,b)	HEF	Plaque reduction	HSV-2	0.27-8.0		
Tocci et al. (1984)	MRC-5	Plaque reduction	HSV-2 (Curtis)	1.6	3.6	
Tyms et al. (1984)	HEF.	Plaque reduction	HSV-2	0.1	0.46	

a PRK = primary rabbit kidney cells; Vero = green monkey kidney cells; BU-BHK = BVDU-resistant baby hamster kidney cells; HFF = human foreskin fibroblasts; HEF = human embryo fibroblasts; MRC-5 = human embryo lung cells; P3HR-1 = Epstein Barr virus-infected human lymphoblastoid cells.

b Results reported in mg/L were converted to μmol/L. Results were reported as ID_{50}, ED_{50} or CPE_{50} values = drug concentration inhibiting viral plaques or virus-induced cytopathogenicity by 50%.

c Four laboratory strains (Schooler, S, McIntyre, McKrae).

d Assays performed in various cell lines.

hybridisation assay of 5 human cytomegalovirus clinical isolates revealed limited synergy between zidovudine and ganciclovir with ganciclovir having an ID_{50} of 4.2 μmol/L alone and 3.0 μmol/L in combination with zidovudine 12 μmol/L. Combination of ganciclovir with ribavirin or dideoxycytidine did not show increased activity compared with ganciclovir alone (Dankner & Spector 1988).

Herpes Simplex Virus Types 1 and 2

In human embryo fibroblasts a combination of ganciclovir 1.2 mg/L (4.7 μmol/L) with phosphonoacetic acid 250 mg/L (1500 μmol/L) had a synergistic antiviral effect on herpes simplex virus type 1 (Patton), reducing virus titre by over 50-fold more than what would be expected if their effects were additive; ganciclovir 0.7 mg/L (2.7 μmol/L) in combination with foscarnet 90 mg/L (450 μmol/L) reduced virus titre by more than 200-fold compared with their calculated additive effects. Similar effects were observed against clinical isolates of herpes simplex virus type 2 *in vitro*, with ganciclovir 2.0 mg/L (7.8 μmol/L) in combination with phosphonoacetic acid 76 to 90 mg/L (450 to 600 μmol/L) producing a 20- to 70-fold reduction in virus titre compared with the calculated additive effect, and ganciclovir 0.7 mg/L (2.7 μmol/L) or 30 mg/L (118 μmol/L) in combination with foscarnet 80 mg/L (400 μmol/L) producing over a 4000-fold and a 55-fold reduction in viral titre of 2 clinical isolates, respectively, compared with the calculated additive effects (Smith et al. 1982b). However, combinations of ganciclovir with BVDU, aciclovir or vidarabine against herpes simplex virus types 1 or 2 *in vitro* showed additive or only limited synergistic effects (Moran et al. 1985; Smith et al. 1982b).

The interferons have also been evaluated for synergy with ganciclovir in *in vitro* models of herpes simplex virus infection. In human foreskin fibroblasts a combination of ganciclovir 0.01 mg/L (0.04 μmol/L) with recombinant human interferon-α A 22 U/ml provided 50% inhibition of cytopathogenicity caused by herpes simplex virus type 1 (E-377), whereas when used alone recombinant human interferon-α A 210 U/ml or ganciclovir 0.07

Table III. Summary of the *in vitro* activity of ganciclovir and aciclovir against Epstein-Barr virus (EBV), varicella zoster virus (VZV), human herpesvirus 6 (HHV-6), adenovirus (AdV) and vaccinia virus

Reference	Cell culture[a]	Viral assay method	Virus (strain)	Concentration achieving 50% inhibition[b] (μmol/L)	
				ganciclovir	aciclovir
Agut et al. (1989); Russler et al. (1989)[c]	PMN	Immunofluorescence/ DNA hybridisation	HHV-6	1.1	18-45
		Cytopathogenicity		2-3.8	100
Collins & Oliver (1985)	MRC-5	Plaque reduction	VZV (Fortier)	3.71	2.09
Field et al. (1983)	HCL	Transformation inhibition	EBV	4.5-22.3	>50-500
	MRC-5	Plaque reduction	VZV (KMcC)	4.5-9	5-10
	PRK	Plaque reduction	Vaccinia	>450	>500
Lin et al. (1984, 1985); Pagano et al. (1983)[d]	P3HR-1	Genome replication	EBV	0.05	0.3
Smith et al. (1982a)	HR, K(33)	Antigen expression	EBV	125	
	HEF	Plaque reduction	VZV (32)	51	
	KB	Antigen expression	AdV2	71	
	HEF	Cytopathogenicity	Vaccinia	>450	
Taylor et al. (1988)	HEF	Plaque reduction	AdV[e]	4.5-33	
Tolman et al. (1985)	MRC-5	Plaque reduction	VZV (KMcC)	10-20	20-40
	GM		AdV2	180	
	MRC-5		Vaccinia	180-360	>400

a MRC-5, = human embryo lung cells; HEF = human embryo fibroblasts; PMN = peripheral blood mononuclear cells; HCL = human cord lymphocytes; PRK = primary rabbit kidney cells; P3HR-1 = Epstein-Barr virus-infected human lymphoblastoid cells; KB = human nasopharyngeal carcinoma cells; GM = green monkey cells.

b Results reported in mg/L were converted to μmol/L. Results were reported as ID_{50} or ED_{50} values = drug concentration inhibiting viral plaques, DNA synthesis, transformation, antigen expression or virus-induced cytopathogenicity by 50%.

c In these studies the ID_{50} for foscarnet was 8.7 μmol/L.

d In these studies the ID_{50} values for bromovinyldeoxyuridine and 2′-fluoro-5-iodoarabinosylcytosine were 0.06 and 0.005 μmol/L, respectively.

e 5 genotypes including 12 serotypes.

mg/L (0.27 μmol/L) were required to achieve similar effects. Similar results were observed in herpes simplex virus type 2 (MS) infection where recombinant human interferon-α A 43 U/ml in combination with ganciclovir 0.03 mg/L (0.12 μmol/L) resulted in 50% viral inhibition compared with 940 U/ml or 0.3 mg/L (1.2 μmol/L), respectively, of each agent alone (Moran et al. 1985). Another study indicated that ganciclovir in combination with interferon-α or -β resulted in a 40- to 100-fold reduction in herpes simplex virus type 2 yield, whereas a combination with interferon-γ produced a 3-fold reduction in viral yield *in vitro* (Fraser-Smith et al. 1984a). A study evaluating herpes simplex virus type 2 (G) infection in human embryo tonsil cells found that maximum synergistic antiviral effects with ganciclovir 0.007 mg/L (0.027 μmol/L) occurred at a concentration of 200 U/ml for recombinant human interferon-α_1, -α_2, -β ser-17 or -γ, with 80-, 35-, 350- and 2.5-fold inhibition of virus, respectively, compared with the calculated additive effects. Ganciclovir in combination with recombinant human interferon-β ser-17 almost completely eliminated infectious virus production. Ganciclovir exhibited up to 5-fold greater synergism with interferons than did aciclovir and it was suggested this may in part explain the greater *in vivo* efficacy of ganciclovir compared

with aciclovir (section 1.2; Eppstein & Marsh 1984).

1.2 Antiviral Activity *In Vivo*

Animal models of herpes simplex virus type 1 or 2 infections are well established and ganciclovir has been evaluated in a variety of *in vivo* situations. However, an *in vivo* model of human cytomegalovirus infection has not been developed and results of ganciclovir treatment in other cytomegalovirus infections in animals are of limited usefulness in predicting the clinical efficacy against the corresponding human infections, particularly as some of these viruses encode a thymidine kinase (section 1.3). Indeed, for many viral infections results of *in vivo* studies in animals are of limited predictive value for the antiviral efficacy of an agent in humans, with the therapeutic outcome being influenced by animal species, virus strain, inoculum size, drug dose and administration route, and the time lag between infection and initiation of antiviral therapy. In many studies therapy is withheld for several days or until symptoms of viral infection appear in an attempt to more closely model the clinical situation. These variables also make interstudy comparisons difficult.

The effects of ganciclovir on establishment and maintenance of viral latency have also been investigated in a few studies – although currently available antiviral agents cannot prevent establishment of latent viral infection in neuronal ganglia, by limiting infectious virion production they may reduce acute ganglionic infection, and inhibit virus migration to the brain and subsequent encephalitis, thereby improving overall survival (Katzenstein et al. 1986).

1.2.1 Cytomegalovirus Infections

Encephalitis and Disseminated Infection

In acute lethal murine cytomegaloviral infections ganciclovir 10 to 100 mg/kg/day by various routes of administration reduced mortality, as did aciclovir 25 mg/kg (Duke et al. 1986; Freitas et al. 1985; Kern et al. 1984).

Subcutaneous or intraperitoneal ganciclovir 100 mg/kg/day from 24 hours after infection prevented clinical disease but delay of treatment initiation to 48 or 72 hours resulted in a progressive increase in mortality (Katzenstein et al. 1986). In immunosuppressed mice higher ganciclovir dosages were required to increase survival compared with immunocompetent animals. A combination of ganciclovir with murine cytomegalovirus antiserum was more effective than either agent alone (Rubin et al. 1989; Wilson et al. 1987). Ganciclovir has also shown efficacy in the treatment of acute guinea-pig cytomegalovirus infection (Fong et al. 1987). Ganciclovir did not appear to prevent establishment of latent murine cytomegalovirus infection and did not reduce viral titres in the liver, heart or salivary glands following reactivation (Wilson et al. 1987).

Pulmonary Infections

Interstitial pneumonitis associated with cytomegalovirus infection is believed to have an immunological component (Grundy et al. 1987). However, studies in mice have provided some indication that antiviral therapy with ganciclovir may be beneficial (Debs et al. 1988; Shanley et al. 1985, 1988). In these murine models systemic or aerosolised ganciclovir produced dose-proportional reductions in viral titres in lung tissue and salivary glands (systemic administration only), and was more potent than aciclovir. However, neither ganciclovir nor aciclovir prevented development of pneumonitis.

Cytomegalovirus Prophylaxis

Limited data suggest prophylactic ganciclovir therapy may prevent cytomegalovirus infection. Intrathecal cytomegalovirus inoculation of guinea-pigs produces cochlear inflammation and hearing loss similar to the sensorineural hearing loss observed after congenital human cytomegalovirus infection. Animals receiving intraperitoneal ganciclovir 100 mg/kg twice daily for 9 days from 1 day before infection showed normal cochlear and brain morphology and normal cochlear pathophysiology compared with uninfected guinea-pigs. Infected

animals not receiving ganciclovir showed acute labyrinthitis, meningitis and a mean increase of 17 decibels in the auditory nerve compound action potential threshold. However, it was not established whether ganciclovir prevented or only suppressed infection during active treatment (Woolf et al. 1988).

1.2.2 Herpes Simplex Virus Types 1 and 2

Encephalitis and Disseminated Infections

Ganciclovir has shown considerable efficacy in murine models of herpes simplex virus encephalitis following oral, subcutaneous or intraperitoneal administration, with lower doses (0.8 mg/kg/day or more) increasing mean survival time and higher dosages (50 mg/kg/day) increasing survival to 100% (Ashton et al. 1982; Collins & Oliver 1985; Field et al. 1983, 1984; Kern et al. 1984; Smee et al. 1985b). Treatment may be delayed to up to 96 hours postinfection while maintaining a significant decrease in mortality at higher dosages, but early institution of therapy reduces morbidity and increases survival (Field et al. 1984; Kern et al. 1984). In general, effective ganciclovir dosages in type 2 infections are about 3- to 10-fold higher than those producing a significant effect in type 1 infections (Ashton et al. 1982; Collins & Oliver 1985; Field et al. 1983, 1984; Kern et al. 1984; Smee et al. 1985b). Ganciclovir therapy of herpes simplex virus type 1 encephalitis did not appear to prevent establishment of latent viral infection, with most animals having latent virus in the trigeminal ganglia following recovery from acute infection after ganciclovir or aciclovir therapy (Field et al. 1984).

FMAU has shown efficacy similar to that of ganciclovir in both type 1 and type 2 encephalitis (Smee et al. 1985b) but aciclovir, FIAC, BVDU, foscarnet and vidarabine, where evaluated, were markedly less effective at similar dosages (Ashton et al. 1982; Collins & Oliver 1985; Field et al. 1983, 1984; Smee et al. 1983, 1985b).

In mice with systemic herpes simplex virus type 2 infection, the synergistic antiviral effects of ganciclovir in combination with recombinant human interferon-α or recombinant human interferon-β were similar to those observed *in vitro*, with about a 10-fold reduction in the 50% effective dose (ED_{50}) of each agent. However, recombinant murine interferon-γ was considerably more potent in combination with ganciclovir *in vivo* compared with interferon-α or -β, or with *in vitro* results, suggesting host antiviral responses may be potentiated by this combination (section 1.1.4; Fraser-Smith et al. 1984a,b, 1985).

Genital Infections

Limited data from *in vivo* studies of herpes simplex virus type 2 vaginal infection in mice and guinea-pigs suggest that systemically or topically administered ganciclovir is effective in both primary and recrudescent infections and is more potent than aciclovir in these models (Field et al. 1983; Smee et al. 1983, 1985b). In a guinea-pig model there was some evidence that immediate institution of ganciclovir therapy after primary infection may partially inhibit establishment of ganglionic latency, but ganciclovir was not effective in eradicating latent viral infection (Fraser-Smith et al. 1983).

Ocular Infections

Studies in New Zealand white rabbits indicate that topical ganciclovir ointment of at least 0.1% concentration 3 times daily, or eye drop solution of at least 0.06% concentration 5 times daily, significantly decreases the duration of viral shedding, corneal epithelial involvement, and clouding, conjunctivitis and iritis, compared with placebo in eyes infected with herpes simplex virus type 1 when treatment is given from 3 days after infection (Davies et al. 1987; Smith et al. 1984; Trousdale et al. 1984). However, viral colonisation of the trigeminal ganglia was not prevented. Treatment from 1 hour postinfection did prevent the establishment of latency but this finding does not parallel the clinical situation (Trousdale et al. 1984).

Evaluation of ganciclovir 100μg as an ophthalmic insert dissolving in 1 hour, and administered for 4 days from 3 days postinfection, indicated that lesion development was reduced compared with placebo and stromal clouding was

prevented, while no signs of irritation were noted in uninfected treated eyes. Ganciclovir eye drops were 6.4-fold more potent than aciclovir eye drops in herpes simplex virus type 1 ophthalmic infections with aciclovir 3% having an efficacy similar to that of trifluridine 1% (Davies et al. 1987). Topical ganciclovir ointment 0.3% 5 times daily or 1% 3 times daily were of greater or equivalent efficacy, respectively, compared with aciclovir 3% 3 times daily and better than idoxuridine 0.5% ointment (Shiota et al. 1987; Trousdale et al. 1984).

Orofacial Infections

In hairless immunocompetent mice with a sublethal localised herpes simplex virus type 1 infection induced by inoculation onto snout abrasions, inflammation is observed by day 5, followed by vesicle formation. Oral ganciclovir was found to be 6.9-fold more potent than oral aciclovir in this model and showed efficacy when treatment was delayed for up to 72 hours after infection, whereas aciclovir was only effective if treatment was begun 3 hours after infection (Davies et al. 1983, 1984; Field et al. 1983). Virus reactivation studies in trigeminal ganglia explants indicated oral ganciclovir 12.5 mg/kg/day provided some protection against latent infection when begun as late as 24 hours after viral inoculation (Davies et al. 1984). Topical ganciclovir also significantly reduced lesion severity in a dose-proportional and time-proportional manner if treatment was delayed for up to 72 hours after infection, with a 5% cream twice daily for 4 days from 24 hours postinfection completely preventing skin lesions. The frequency of latent ganglionic infection was reduced by this regimen and also by ganciclovir as a 1% solution given as 11 treatments over 3 days from 24 hours postinfection (Davies et al. 1984; Klein & Friedman-Kien 1985). Topical ganciclovir 5% cream twice daily for 4 days from 6 hours after infection prevented the establishment of latent ganglionic infection (Klein & Friedman-Kien 1985).

1.3 Mechanism of Action

Intracellular phosphorylation of ganciclovir to the triphosphate derivative, which acts as a competitive inhibitor of deoxyguanosine triphosphate

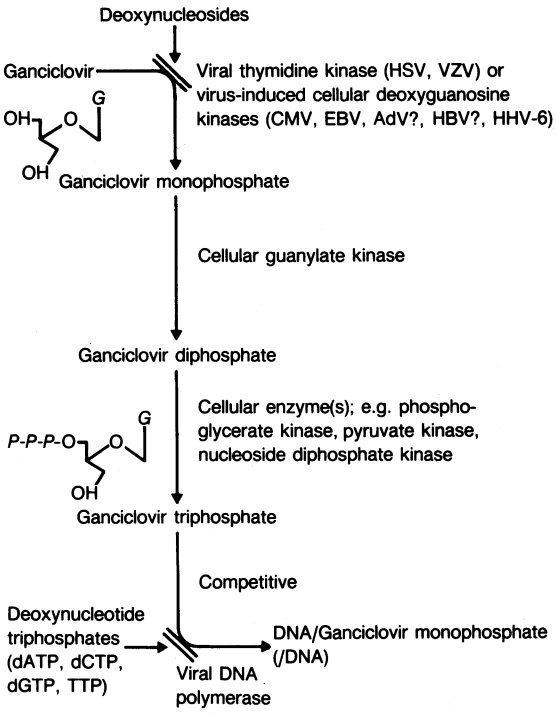

Fig. 2. Ganciclovir inhibition of viral DNA synthesis. Ganciclovir competes with deoxynucleosides for viral thymidine kinase or cellular kinases. In addition to competitively inhibiting the association of deoxynucleoside triphosphates with viral DNA polymerase, ganciclovir triphosphate is incorporated into the growing viral DNA chain, markedly reducing the rate of DNA synthesis (adapted from O'Brien & Campoli-Richards 1989). *Abbreviations:* HSV = herpes simplex virus; VZV = varicella zoster virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus; AdV = adenovirus; HBV = hepatitis B virus; HHV-6 = human herpesvirus 6; *G* = guanosine group; *P* = phosphate group.

thus inhibiting viral DNA synthesis, is required for antiviral activity (fig. 2; Cheng et al. 1983a; Field et al. 1983). In cells infected with herpes simplex or varicella zoster virus the mechanism of phosphorylation appears to be similar to that described for aciclovir (Biron et al. 1985; Cheng et al. 1983b; Germershausen et al. 1983; Mar et al. 1985; Smee et al. 1985a), with viral thymidine kinase catalysing production of the ganciclovir monophosphate derivative (Ashton et al. 1982; Field et al. 1983). However, human cytomegalovirus does not en-

code a viral thymidine kinase (Estes & Huang 1977), and although Epstein-Barr virus appears to have some degree of thymidine kinase activity (Littler et al. 1986) monophosphorylation of aciclovir in infected cells is poor (reviewed in O'Brien & Campoli-Richards 1989). Cellular thymidine kinases do not catalyse ganciclovir monophosphorylation and phosphorylation of ganciclovir in uninfected cells is minimal (Field et al. 1983; Freitas et al. 1985).

In cells infected with human cytomegalovirus, production of ganciclovir monophosphate appears to be catalysed by an induced host-encoded deoxyguanosine kinase (Biron et al. 1985; Smee 1985). Monophosphorylation of ganciclovir probably occurs by similar mechanisms in cells infected with other DNA viruses against which ganciclovir shows some activity (sections 1.1.3 & 1.2; Smee 1985; Smee et al. 1985c; Taylor et al. 1988). Subsequent formation of the diphosphate and triphosphate ganciclovir derivatives is catalysed by cellular guanylate kinase (Boehme et al. 1984; Cheng et al. 1983a; Smee et al. 1985a), and by several cellular kinase enzymes, but primarily phosphoglycerate kinase (Smee et al. 1985a), respectively.

Several features of ganciclovir anabolism facilitate its antiviral efficacy. Uptake of ganciclovir into cells infected with herpes simplex virus type 1 was markedly greater than ganciclovir uptake in uninfected cells and also greater than uptake of aciclovir under similar conditions (Cheng et al. 1983a; Germershausen et al. 1983), although the mechanism underlying this has not been determined. Possibly rapid phosphorylation of ganciclovir by virus-encoded or virus-induced kinase enzymes shifts the equilibrium, resulting in increased ganciclovir uptake. Additionally, ganciclovir appears to be a better substrate for both the virus-encoded and the host-encoded kinase enzymes involved in nucleoside phosphorylation than aciclovir (Ashton et al. 1982; Biron et al. 1985; Field et al. 1983; Germershausen et al. 1983; Smee et al. 1985a; St Clair et al. 1984). This has been attributed to the structural similarity of ganciclovir, which possesses equivalents of both the 3′ and 5′ hydroxyl groups, to endogenous nucleosides (fig. 1). However, production of ganciclovir triphosphate in uninfected cells was up to 100-fold less than that in cells infected with human cytomegalovirus, with the rate of ganciclovir triphosphate formation depending on the extracellular ganciclovir concentration and the multiplicity of infection (Biron et al. 1985). This finding, coupled with apparent preferential affinity of ganciclovir triphosphate for virus-encoded, as compared with host-encoded, DNA polymerase (table IV; Cheng et al. 1984; Germershausen et al. 1983), suggests relative specificity of action of ganciclovir in infected compared with healthy cells. Indeed, as shown in table IV, the binding affinity of aciclovir triphosphate for cellular DNA polymerase alpha enzymes is usually much higher than that of ganciclovir triphosphate, reducing the relative selectivity of aciclovir triphosphate.

The triphosphates of ganciclovir and aciclovir may inhibit DNA polymerases by different mechanisms, as herpesvirus DNA polymerase mutants resistant to aciclovir often remain susceptible to ganciclovir (section 1.4). Increased uptake and rate of phosphorylation of ganciclovir in infected compared with uninfected cells, and the specific inhibition of viral DNA polymerase by ganciclovir triphosphate, contribute to the marked differences in ganciclovir concentrations inducing cytopathic effects in herpesvirus-infected and uninfected cells treated with ganciclovir (section 1.1 and section 2). Although ganciclovir triphosphate has a lower binding affinity for the DNA polymerase encoded by human cytomegalovirus than does aciclovir triphosphate, production and stability of ganciclovir triphosphate in cells infected with human cytomegalovirus is much enhanced compared with aciclovir triphosphate (Biron et al. 1985).

Unlike aciclovir, ganciclovir does not act as an absolute chain terminator following incorporation into DNA by polymerase enzymes, with several authors reporting internal incorporation of ganciclovir into DNA (Cheng et al. 1983a; Frank et al. 1984; St Clair et al. 1987). Ganciclovir has hydroxyl groups analogous to both the 3′ and 5′ hydroxyl groups found in endogenous nucleosides (fig. 1) permitting continued chain elongation following

Table IV. Kinetic constants for cellular DNA polymerase α and virus-induced DNA polymerases

Reference	DNA polymerase α	Km dGTP (nmol/L)	K_i (nmol/L)	
			ganciclovir	aciclovir
Herpes simplex virus type 1-induced enzyme				
Frank et al. (1984)	HSV-1 (KOS)	235	33	3[a]
Smee et al. (1985a)	HSV-1 (F strain)		90	3
St Clair et al. (1984)	HSV-1 (KOS)	170	50	6
	HSV-1 (Patton)	180	80	6
	HSV-1 (PAA^R5)[b]	680	50	130
	HSV-1 (BW^R)[b]	610	50	530
Herpes simplex virus type 2-induced enzyme				
Frank et al. (1984)	HSV-2	120	46	3[a]
Human cytomegalovirus-induced enzyme				
Biron et al. (1985)	HCMV (AD169)		1400	330
Freitas et al. (1985)	HCMV (AD169)		1700	300
Mar et al. (1985)	HCMV (Towne)	470	22	8
Cellular enzyme (not virus-induced)				
Frank et al. (1984)	Peripheral blasts (AML)	800	125	
Freitas et al. (1985)	MRC-5[c]		17000	
Mar et al. (1985)	WI-38[d]	1430	146	96
Smee et al. (1985a)	HeLa[e]		4200	440
St Clair et al. (1984)	HeLa S-3[e]	1200	2500	370

a From Derse et al. (1981).
b Aciclovir-resistant strains; PAA^R5 is an HSV-1(KOS)mutant and BW^R is an HSV-1 (Patton) mutant.
c Human embryonic lung cells.
d Human fibroblasts.
e Human cervical carcinoma cells.
Abbreviations: Km = Michaelis-Menten constant; dGTP = deoxyguanosine triphosphate; K_i = competitive inhibition constant against dGTP; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type 2; HCMV = human cytomegalovirus; AML = acute myelogenous leukaemia.

its incorporation into DNA. However, DNA with ganciclovir monophosphate at the 3′ terminus is a poor substrate for continued chain elongation. The competitive inhibition constant of ganciclovir monophosphate-terminated DNA has been calculated as 1.5 nmol/L (Frank et al. 1984) which is similar to the 2.1 nmol/L reported for DNA terminated by aciclovir monophosphate (Derse et al. 1981), and incorporation of ganciclovir into DNA reduces the rate of chain elongation to levels below those observed in reactions not including deoxyguanosine triphosphate (Frank et al. 1984; Mar et al. 1985).

Prevention of viral DNA synthesis by incorporation of ganciclovir into the replicating strand blocks late gene expression and protein synthesis by the virus, inhibiting production of viral progeny (Chun & Park 1987; Tocci et al. 1984; Tyms et al. 1987). However, viral replication resumes, indicating reversible virostatic inhibition, following removal of ganciclovir from the culture medium (Mar et al. 1983).

The effect of internal ganciclovir monophosphate incorporation on the rate and accuracy of transcription by RNA polymerase enzymes, and the role of exonuclease and endonuclease enzymes in excision of ganciclovir from DNA, do not appear to have been evaluated.

1.4 Viral Resistance to Ganciclovir

Ganciclovir-resistant strains of herpes simplex virus or human cytomegalovirus may be developed *in vitro* by serial passage in subinhibitory concentrations of drug (Biron et al. 1986; van der Horst et al. 1987), presumably by selection of viruses with relatively low drug susceptibility. Relatively ganciclovir-resistant herpesvirus strains have also been reported in pretherapy clinical isolates (Erice et al. 1989; Plotkin et al. 1985; Shepp et al. 1985) and following ganciclovir (Erice 1988; Erice et al. 1989) or aciclovir (McLaren et al. 1985) therapy.

Mutations in viral thymidine kinase and/or DNA polymerase genes appear to mediate development of resistance in herpes simplex viruses (reviewed by O'Brien & Campoli-Richards 1989). Mutations in the viral thymidine kinase gene may result in thymidine kinase-deficient mutants that induce little or no enzyme activity and that are usually resistant to most agents requiring phosphorylation by this enzyme for antiviral activity, including ganciclovir and aciclovir (Cheng et al. 1983b; Collins & Oliver 1985; McLaren et al. 1985). Alternatively, thymidine kinase mutants with an altered substrate specificity which no longer effectively phosphorylate ganciclovir may result and these may or may not exhibit cross-resistance to aciclovir (Cheng et al. 1983b; McLaren et al. 1985). Viral DNA polymerase-mediated resistance is usually the result of selection of mutants encoding an altered enzyme and aciclovir-resistant mutants of this type often retain sensitivity to ganciclovir (Coen et al. 1985; Smee et al. 1983). The mechanism of ganciclovir resistance in human cytomegalovirus infections may also involve mutation in the viral DNA polymerase gene although a human cytomegalovirus ganciclovir-resistant mutant has been described which retained wild type sensitivity to viral DNA polymerase inhibitors (foscarnet, aphidicolin, FIAC, vidarabine and PAA), but was associated with reduced production of ganciclovir diphosphate and triphosphate derivatives despite unaltered ganciclovir uptake and ganciclovir triphosphate stability (Biron et al. 1986). This mutant may not induce adequate levels of the virus-induced host-encoded deoxyguanosine kinase enzyme suggested to be required for the conversion of ganciclovir to ganciclovir monophosphate.

Thymidine kinase-deficient isolates of herpes simplex virus exhibit reduced neurovirulence *in vivo* with reduced infectivity, pathogenicity and establishment of latency, whereas thymidine kinase mutants with altered substrate specificity and DNA polymerase mutants usually retain wild type virulence (reviewed in O'Brien & Campoli-Richards 1989). Continued monitoring is required to further define the rate of occurrence and clinical significance of viral resistance to ganciclovir.

2. *Toxicology Studies*

In most human cells *in vitro* ganciclovir concentrations resulting in host cell toxicity are many times greater than those required for antiviral activity, although cells with a high rate of DNA synthesis including haemopoietic progenitor cells appear to be particularly sensitive to ganciclovir (table V; Bowden et al. 1987; Sommadossi & Carlisle 1987). In a toxicity trial of prophylactic ganciclovir following total body irradiation and autologous marrow transplant in dogs, intravenous ganciclovir 3 mg/kg/day was well tolerated, whereas 5 mg/kg/day was associated with a delayed recovery of platelet counts but not absolute neutrophil counts (Applebaum et al. 1988).

In toxicity studies in New Zealand white rabbits intravitreal injection of ganciclovir up to 450μg did not produce detectable ophthalmoscopic, histological or electroretinographical changes, and maintained vitreous ganciclovir levels above ID_{50} levels for herpesviruses for up to 60 hours (Pulido et al. 1985; Schulman et al. 1986a,b). Similarly, intravitreally injected liposomes containing the equivalent of ganciclovir 94μg and trifluridine 102μg maintained vitreous drug concentrations above ID_{50} values for herpes simplex virus types I and II and cytomegalovirus for at least 14 days in rabbit eyes without observable retinal toxicity (Peyman et al. 1989). However, some ocular changes were observed following administration of 3% gan-

Table V. Cytotoxic effects of ganciclovir on human cells *in vitro*. Lack of inhibitory effects on normal cell function is reported as nontoxic at the concentrations noted

Reference	Cell culture[a]	Assay method	Result (ganciclovir concentration; μmol/L)[b]
Baba et al. (1986)	HEF	Cell viability	Nontoxic (500)
Cheng et al. (1983b)	HeLa S_3	Cell proliferation	ID_{50} = 125
	WI-38		Nontoxic (50)
	P3HR-1		ID_{50} = 40
Freitas et al. (1985)	MRC-5	Cell proliferation	ID_{50} = 110
	HET		ID_{50} = 250
Lin et al. (1984, 1985)	P3HR-1	Cell proliferation	ID_{50} = 200
Pulliam et al. (1986)	BEC	Cell morphology	Nontoxic (800)
Smith et al. (1982a)	HEF	Cell proliferation	ID_{50} = 125
		^{3}H-thymidine uptake	ID_{50} = 1800
Sommadossi & Carlisle (1987)	BFU-E	Colony formation	ID_{50} = 1.6
			ID_{90} = 100
	CFU-GM		ID_{50} = 2.7
			ID_{90} = 35.7

a HEF = human embryo fibroblasts; HeLa S_3 = human cervical carcinoma cells; WI-38 = human fibroblasts; P3HR-1 = human lymphoblastoid cells; MRC-5 = human embryo lung cells; HET = human embryo tonsil cells; BEC = embryo brain cell aggregates; BFU-E = burst-forming units-erythroid; CFU-GM = colony-forming units granulocyte macrophage.

b Results reported in mg/L were converted to μmol/L; ID_x = concentration of ganciclovir required to inhibit the measured value by X%.

ciclovir ointment 5 times daily for 2 weeks, consisting of a small increase in dark cells on the corneal surface which was considered negligible (Naito et al. 1988). Ganciclovir administered in vitrectomy infusion solution at concentrations greater than 40 mg/L (155 μmol/L) was associated with local degeneration of retinal cells or disorganisation of retinal layers and electroretinograph abnormalities (Kao et al. 1987). Other toxicology studies in animals and *in vitro* indicate ganciclovir administration may be associated with aspermatogenesis, mutagenicity, teratogenicity, carcinogenicity, bone marrow depression and adverse effects on the gastrointestinal mucosa (data on file, Syntex).

3. *Pharmacokinetic Studies*

The pharmacokinetic properties of ganciclovir have been evaluated in immunocompromised patients with cytomegalovirus infections including transplant recipients, patients receiving chemotherapy for cancer, and patients with acquired immune deficiency syndrome (AIDS). Significant dosage reductions are recommended in patients with a decreased rate of creatinine clearance as the terminal half-life and maximum plasma concentrations of ganciclovir increase with increasing renal impairment (section 3.4; section 7). Similar effects would be expected in infant and elderly patients, who also often have reduced renal function, although studies in these particular groups had not been published at the time of writing. The pharmacokinetic properties of ganciclovir following intravitreal administration in immunocompromised patients with sight-threatening cytomegalovirus retinitis and associated risk factors excluding the patient from intravenous therapy, have been assessed in a limited number of patients.

Reverse-phase high performance liquid chromatography (HPLC) is the most commonly used method of quantifying ganciclovir concentrations in body fluids, with the limit of detection at wavelength 254nm reported as 0.4 μmol/L (100 ng/ml) [Sommadossi & Bevan 1987]. A radioimmunoassay with a sensitivity limit of 3 nmol/L (Nerenberg et al. 1986), and enzyme-linked immunosorbent assay (ELISA) systems (Shepp et al. 1985; Tadepalli et al. 1986) with a reported sensitivity limit of 0.4 μmol/L (Henry et al. 1987a) have also been developed, and provide results similar to those obtained with HPLC (Henry et al. 1987a; Sommadossi et al. 1988).

3.1 Absorption and Plasma Concentrations

3.1.1 Intravenous Administration

Intravenous ganciclovir is usually administered as a 1-hour infusion and displays pharmacokinetics best described by a 2-compartment open model

(Fletcher et al. 1986; Sommadossi et al. 1988; Weller et al. 1987). The pharmacokinetics of intravenous ganciclovir 1 to 5 mg/kg 8-hourly appear to be dose-independent (Laskin et al. 1987a) and mean peak ganciclovir concentrations vary in approximately linear fashion over this dose range (Erice et al. 1987; Felsenstein et al. 1985; Harbison et al. 1988; Laskin et al. 1987b; Sommadossi et al. 1988; Syntex, data on file). Steady-state peak plasma concentrations achieved with an 8-hourly ganciclovir dosage regimen (9.4, 20.3 and 44.5 μmol/L, respectively, at 1.0, 2.5 and 5.0 mg/kg dosages; Laskin et al. 1987a) are similar to those seen after equivalent single doses. This indicates ganciclovir accumulation is unlikely in patients with normal renal function receiving an 8-hourly dosage regimen (Laskin et al. 1987a) – indeed, accumulation did not occur in patients with essentially normal renal function receiving 8-hourly ganciclovir for up to 24 days (Felsenstein et al. 1985; Fletcher et al. 1986; Laskin et al. 1987b; Sommadossi et al. 1988; Syntex, data on file). Steady-state trough ganciclovir plasma concentrations were 0.9, 2.7 and 4.4 μmol/L, respectively, after 1.0, 2.5 and 5 mg/kg 8-hourly (Laskin et al. 1987a). At the higher doses these values are above the reported ID_{50} values of many human cytomegalovirus isolates (table I).

3.1.2 Intraocular and Oral Administration

The pharmacokinetics of intravitreal ganciclovir administration have been studied in 1 patient who received 5 doses of 200μg in a volume of 0.1ml over 15 days. The concentration of ganciclovir in intravitreal fluid immediately following injection was 65 μmol/L, while plasma ganciclovir concentrations remained below the limits of detection of the assay system used (less than 0.4 μmol/L) [Henry et al. 1987a].

Administration of ganciclovir 10 mg/kg as a single oral dose to 6 patients produced peak plasma levels of 0.9 to 1.93 μmol/L about 1.5 hours after administration. The mean bioavailability of oral ganciclovir at this dosage was calculated to be 6% (range 5.4 to 7.1%) based on the urinary recovery rate (De Miranda et al. 1986). Oral ganciclovir 10 or 20 mg/kg every 6 hours in 4 patients resulted in maximum ganciclovir plasma concentrations of 2.01 and 2.96 μmol/L, respectively, 30 to 60 minutes after administration, with minimum plasma concentrations of 0.87 and 1.05 μmol/L, respectively, at 6 hours. Oral bioavailability of the 10 mg/kg dosage as calculated by urinary recovery or comparison of the area under the plasma concentration *vs* time curve was 4.6% or 3.5%, respectively; oral bioavailability of the 20 mg/kg dosage was 3% or 2.5%, respectively (Jacobson et al. 1987).

3.2 Distribution

Autopsy studies were performed on 6 leukaemia patients who died of disease complications on days 4 to 15 of ganciclovir therapy [2.5 (n = 3) or 5 (n = 3) mg/kg 8-hourly as a 1-hour intravenous infusion] for cytomegalovirus pneumonia. Concentrations of ganciclovir in the lung, liver and testes of patients were approximately equal to those found in heart blood. The mean ganciclovir concentration in the CNS was 38% of the mean heart blood concentration whereas concentrations in the kidney were 3- to 7-fold greater than those in heart blood (Shepp et al. 1985).

Furthermore, concentrations of ganciclovir in CSF were 0.68 mg/L (2.7 μmol/L) 3.5 hours after intravenous administration of a 2.5 mg/kg dose [plasma concentrations were predicted to be 2.2 mg/L (8.6 μmol/L); 31% penetration]. While the ratio of CSF to plasma ganciclovir concentration was higher (67%) 5.67 hours after ganciclovir administration, the actual CSF ganciclovir concentration was similar [0.62 mg/L (2.4 μmol/L) Fletcher et al. 1986]. A CSF ganciclovir concentration of 2.4 μmol/L was reported in a patient 1 hour after receiving intravenous ganciclovir 1 mg/kg, when serum ganciclovir was 5.8 μmol/L (41% penetration) [Laskin et al. 1987b].

Distribution of ganciclovir into ocular fluids has also been evaluated. In a bone marrow transplant patient with cytomegalovirus retinitis, subretinal fluid ganciclovir concentrations of 7.16 μmol/L and 2.58 μmol/L were found 5.5 and 8 hours, respectively, after the start of a 1-hour infusion of ganciclovir 5 mg/kg, with corresponding plasma con-

centrations of 8.16 μmol/L and 1.28 μmol/L (Jabs et al. 1986). Pharmacokinetic studies in a further patient with cytomegalovirus retinitis, receiving maintenance intravenous ganciclovir 6 mg/kg/day 5 days/week, revealed ganciclovir concentrations in subretinal and aqueous fluids of 3.6 and 2.4 μmol/L, respectively, 2.5 hours after drug administration when serum ganciclovir was 6 μmol/L. Vitreous fluid ganciclovir concentration 21 hours after administration was 0.8 μmol/L, while serum ganciclovir was undetectable by HPLC at that time (Jabs et al. 1987).

Ganciclovir is 1 to 2% bound to plasma proteins (Syntex, data on file). Studies evaluating the transfer of ganciclovir to breast milk have not been published although considering its wide tissue distribution, low plasma protein binding, and structural similarity to aciclovir, which is found in human breast milk in significant concentrations (reviewed in O'Brien & Campoli-Richards 1989), it seems likely that at least some accumulation in milk occurs. Indeed, ganciclovir concentrations in breast milk may possibly be several times higher than plasma concentrations, although the lack of data on oral bioavailability of the drug in infants means it is impossible to assess the likely effects of this. Similarly, studies evaluating the pharmacokinetics of maternal-fetal transfer of ganciclovir do not appear to have been performed although the teratogenicity of ganciclovir observed in animal models (section 2) suggests this could be an important consideration.

The mean volume of distribution of ganciclovir at steady state has been variously reported as 32.8 L/1.73m^2 (Fletcher et al. 1986), 45L (Laskin et al. 1986) and 44.5 L/1.73m^2 (Weller et al. 1987) following intravenous administration to patients with normal renal function. Following intravitreal ganciclovir administration an apparent volume of distribution in vitreous fluid of 11.7ml has been reported, also suggesting tissue uptake of the drug, possibly by the retina (Henry et al. 1987a).

3.3 Metabolism and Elimination

Almost 100% of intravenously administered ganciclovir is excreted unchanged in the urine in patients with normal renal function (Felsenstein et al. 1985; Laskin et al. 1986, 1987a, 1987b; Shepp et al. 1985; Weller et al. 1987; Syntex, data on file) indicating that little or no extrarenal elimination occurs. Ganciclovir renal clearance is highly correlated with glomerular filtration rate (creatinine clearance), and along with the almost complete urinary recovery of the drug this suggests tubular secretion is involved (Fletcher et al. 1986). Studies in patients with normal renal function receiving intravenous ganciclovir 1 to 5 mg/kg/dose indicate that the elimination half-life ($t_{1/2\beta}$) is 2 to 4 hours (Fletcher et al. 1986; Laskin et al. 1986, 1987a; Shepp et al. 1985; Sommadossi et al. 1988; Weller et al. 1987; Syntex, data on file), and the mean clearance rate has been reported as about 200 ml/min/1.73m^2 (Fletcher et al. 1986; Laskin et al. 1987a; Weller et al. 1987). The half-life of ganciclovir in vitreous fluid following intravitreal administration has been calculated as 13.3 hours (Henry et al. 1987a).

3.4 Pharmacokinetics in Patients with Renal Function Impairment

Several studies have identified that ganciclovir clearance rate decreases in an approximately linear fashion as creatinine clearance decreases, with the rate of ganciclovir clearance being estimated variously as about 1.25- to 2.4-fold the creatinine clearance rate (Fletcher et al. 1986; Laskin et al. 1987a; Metselaar & Weimar 1989; Sommadossi et al. 1988). Thus, the plasma half-life and maximum plasma concentration of ganciclovir increase with increasing renal impairment (Fletcher et al. 1986; Harbison et al. 1988), with a terminal half-life of 9 to 30 hours being reported in patients with a creatinine clearance of 20 to 50 ml/min/1.73m^2 (Weller et al. 1987). In one study a patient with serum creatinine levels of 9.1 mg/dl, and a ganciclovir clearance rate and elimination half-life of 0.23 ml/min/kg and 39.8 hours, respectively, was reported (Sommadossi et al. 1988). Plasma concentrations of ganciclovir are reduced by haemodialysis, with approximately 50% of the dose being removed in 4 hours (Lake et al. 1988; Sommadossi et al. 1988; Syntex, data on file), and a dialysis gan-

ciclovir clearance rate of 68.5 ml/min/1.73m^2 has been reported in 1 patient (Lake et al. 1988).

4. Therapeutic Use in Cytomegalovirus Infections

Ganciclovir has been most widely studied clinically in patients with human cytomegalovirus infections. Immunocompetent individuals with cytomegalovirus infection are usually asymptomatic, but in patients with suppressed or deficient immune function the infection may be associated with considerable morbidity and mortality. Thus, ganciclovir has been used predominantly to treat cytomegalovirus infection in immunologically compromised individuals including patients with AIDS, congenital immunodeficiency, some haematological malignancies, or who have received chemotherapy for malignancy, transplant rejection prophylaxis, or corticosteroid therapy for systemic lupus erythematosus or Crohn's disease. Cytomegalovirus infection occurring *in utero* or in the neonate is also a potentially serious disease as immune function in this patient group is still developing. In a recent case report a neonate with congenital cytomegalovirus infection received ganciclovir 10 mg/kg from 10 days of age. Hepatosplenocardiomegaly regressed. CNS involvement was also suspected and long term follow-up of the child's development was recommended (Muntean et al. 1989). Two infants with cytomegalovirus pneumonia have also been successfully treated with ganciclovir (Fan-Havard et al. 1989). Studies in immunocompromised children or elderly patients have also not been performed although some trials have included such patients among their participants. A retrospective analysis of 12 paediatric transplant recipients with cytomegalovirus infection who received ganciclovir therapy indicated clinical outcome is similar to that of adults with comparable disease (Gudnason et al. 1989). Patients with reduced renal function have been included in many studies with ganciclovir dosage reduced appropriately (section 7).

Cytomegalovirus infection may be generalised, presenting as viruria, viraemia, fever and wasting, and/or may involve specific organs as sites of infection. The underlying cause of immunological compromise appears to influence the site of infection to some extent, with retinitis, adrenalitis and involvement of the gastrointestinal tract being most common in patients with AIDS, whereas pneumonia is a common disease manifestation in bone marrow transplant recipients, and solid organ transplant recipients appear most susceptible to cytomegalovirus hepatitis and pneumonia. Cytomegalovirus nephropathy has been successfully treated with ganciclovir in kidney transplant recipients (for example Ebihara et al. 1989). However, many patients have multiple sites of involvement.

Because ganciclovir has been the only agent to date demonstrating both significant therapeutic efficacy against human cytomegalovirus infection at a wide variety of sites, and acceptable tolerability, it has generally been considered unethical to withhold treatment from patients with life- or sight-threatening disease, many of who have been treated under 'compassionate plea' protocols. Thus, placebo-controlled studies have not been reported, although some authors have compared their results with historical controls and trials including a double-blind methodology are reported to be underway. In addition, many published studies have included patients with varying sites of cytomegalovirus infection and reasons for immunological compromise. Uniform criteria for the assessment of disease response to ganciclovir have not been established, making study comparison difficult. Many patients who die of cytomegalovirus infection do so during induction therapy, indicating the importance of prompt diagnosis and treatment. However, the degree of disease severity before the institution of ganciclovir therapy varies considerably between studies and as results suggest that early initiation of ganciclovir therapy is beneficial, this factor may have a marked effect on patient outcome. The high incidence of serious concomitant infections in immunologically compromised patients has also confounded the assessment of response to ganciclovir therapy; patients may become cytomegalovirus culture-negative but die of superinfection by other organisms. The role of ganciclovir in superinfections is difficult to assess as

although they are common in immunologically compromised patients, ganciclovir therapy has been associated with neutropenia (section 5) and may also have a contributory role. However, there has only been limited evidence of the development of cytomegalovirus resistance to ganciclovir during therapy (Erice et al. 1989), with patients treated for disease relapse usually responding.

With the exception of intravitreal administration in a small number of patients with cytomegalovirus retinitis, ganciclovir has been exclusively administered by the intravenous route as a 1-hour infusion. Although prophylactic ganciclovir has been used successfully in a few patients, prompt institution of therapy following diagnosis of cytomegalovirus infection currently appears to be favoured, predominantly because of the morbidity that may be associated with continuous therapy. The haematological toxicity of ganciclovir (reflecting the sensitivity of haemopoietic cells to the drug) also makes it less attractive than aciclovir in the treatment of herpes simplex virus, varicella zoster virus and herpesvirus simiae, although ganciclovir demonstrates considerable efficacy against these infections both *in vitro* and *in vivo*.

4.1 Cytomegalovirus Retinitis

Cytomegalovirus retinitis is most often observed in patients with AIDS although it may also occur in other immunocompromised patient groups. Careful diagnosis is important with exclusion of other possible aetiologies, including *Toxoplasma gondii*, herpes simplex virus and human immunodeficiency virus (HIV) involvement required. Previously many patients presented with retinitis well advanced as visual loss is often not perceived until damage is extensive. However, as medical personnel have become more aware of the problem, diagnosis is often made before substantial loss of visual acuity occurs. Visual loss is progressive and may be extremely rapid without adequate treatment.

Ganciclovir has usually been administered intravenously although intravitreal injection of the drug has also proved successful in a limited number of patients (section 4.1.2). However, intravenous ganciclovir therapy is preferable as cytomegalovirus retinitis usually occurs in association with disseminated cytomegaloviral disease and intravitreal ganciclovir administration does not provide systemic therapy.

Ophthalmological improvement following ganciclovir administration is not always correlated with an improvement in visual acuity; however, substantial improvements in visual acuity have been observed in some patients, probably in association with resolution of haemorrhages and retinal inflammation. Following a study in 40 patients Holland et al. (1987) concluded that a reduction in retinal opacification, resulting from resolution of oedema and necrotic tissue mobilisation, was the most reliable sign of early disease response, with the success of long term maintenance therapy indicated by a failure of disease borders to advance. An improvement of visual acuity in association with ganciclovir therapy was most often observed in patients with disease adjacent to but not involving the fovea. Autopsies performed on patients with AIDS who died while receiving ganciclovir for cytomegalovirus retinitis have found immature viral capsids, particularly in retinal cells, confirming the virostatic rather than virucidal action of the drug (Pepose et al. 1987; Teich et al. 1988).

Maintenance ganciclovir therapy significantly reduces the relapse rate although breakthrough retinitis may occur even with higher maintenance dosage regimens. This usually responds to repeated induction therapy or an increase in maintenance dosage although this is not always possible because of toxicity (Buhles et al. 1988; Henderly et al. 1987; Jabs et al. 1987; Jacobson et al. 1988c,d; Orellana et al. 1987). In addition, the development of retinitis has also been observed in patients receiving maintenance ganciclovir therapy because of other sites of cytomegalovirus infection (Erice et al. 1987; O'Donnell et al. 1987). As yet there is only limited evidence that ganciclovir therapy of cytomegalovirus retinitis in patients with AIDS prolongs overall survival, although sight is preserved in many instances (Henderly et al. 1987; Jacobson et al. 1988c; Orellana et al. 1987).

4.1.1 Intravenous Ganciclovir Therapy

The response to ganciclovir induction and maintenance therapy in patients with AIDS and cytomegalovirus retinitis appears to be dose-proportional (table VI; Laskin et al. 1987b; Orellana et al. 1987). In addition, deferment of ganciclovir maintenance treatment has been associated with earlier progression of disease and further loss of visual acuity (Jacobson et al. 1988c,d). The rate of response may also be more rapid at higher dosages (Masur et al. 1986). Improvements may be observed as early as the first day of ganciclovir treatment, with maximum improvement reported after a mean of 21.5 days' therapy with ganciclovir 2.5 mg/kg 3 times daily in 1 study (Orellana et al. 1987). Further improvements in ophthalmological findings may be observed during maintenance therapy, probably resulting from continued resolution of residual opacification and exudative material (Holland et al. 1987; Orellana et al. 1987). Results also

Table VI. Some studies comparing different dosages of intravenous ganciclovir for treatment of severe[a] human cytomegalovirus (HCMV) retinitis in patients with acquired immune deficiency syndrome (AIDS)

Reference	Ganciclovir induction therapy[b] [mg/kg/day] (duration)	Ophthamological response[c] (no. of patients)	Ganciclovir maintenance therapy [mg/kg/wk] (no. of patients)	Days to clinical relapse/ disease progression	Comments
Bailleul (1988)	10 (14 days)	79% (263/334)	None (41) 10-20 (10) 25-35 (70)	31 37 145	Includes patients from 3 studies. Relapse rate at 3 months was 100%, 87% and 42%, respectively
Buhles et al. (1988)	None[d] 7.5 or 10 (14 days)[e]	10% (2/20) 84% (85/105)†††,[f]	None (20) 10-15 (9) 25-35 (32)	41 (47)[g] 51 (47) 128* (105)*	Visual acuity had also improved following ganciclovir induction therapy in 27/31 eyes examined
Jacobson et al. (1988c, 1988d)	7.5 (10 days)[e]	85% (22/27)	25 Immediately after induction (8) Deferred until progression (8) Following deferment (6)	 53.8 (2-66)***[h] 18.8 (9-35) 53 (6-89)*	Visual acuity better in patients receiving immediate *vs* deferred maintenance at last evaluation
Laskin et al. (1987a)	3[i] 7.5[i]	0% (0/3) 92% (46/50)	None (21) 7.5-12.5 (15)	30 'Long term'**	Relapse rate at 1 month was 100% 73% relapse rate after 'long term' therapy ($p = 0.02$ *vs* 25-35 mg/kg/wk)
	15[i]	86% (6/7)	25-35 (8)	60††	No relapses after 2 months' follow-up

a As defined by the authors - usually sight-threatening.
b Induction therapy was administered in 2 or 3 divided doses per day.
c Defined as improvement or stabilisation of retinitis based on ophthalmological findings.
d Historical controls.
e Dosage modified according to haematological parameters and/or renal function.
f Patients receiving ganciclovir for ⩾ 10 days and who were HCMV culture-positive at baseline were evaluated.
g Mean (median).
h Median (range).
i For mean 14, range 1-28 days.

Significant differences compared with no/deferred treatment: * $p < 0.05$; ** $p = 0.02$; *** $p = 0.01$; † $p \leqslant 0.004$; †† $p < 10^{-6}$; ††† p = not defined.

suggest that patients with retinitis peripheral to the arcades have a better response than those with posterior pole involvement (Jabs et al. 1987).

In a study of 41 patients with AIDS receiving ganciclovir for cytomegalovirus retinitis, 39 patients reported an improved sense of wellbeing. 33 patients receiving maintenance ganciclovir therapy reported improvements in wellbeing, weight gain, and a reduced incidence of headache and diarrhoea. However, the development of localised perifoveal lesions was noted in 3 eyes of 2 patients although other retinal lesions healed during induction therapy. It was suggested that ganciclovir access to the avascular foveal region may be limited following intravenous administration and that this area may act as a reservoir for cytomegalovirus infection. Intravitreal ganciclovir injection (section 4.1.2) may be an alternative in this instance, bringing the foveal lesions into contact with the drug and preventing their progression (Orellana et al. 1987).

The use of granulocyte-macrophage colony-stimulating factor (GM-CSF) in combination with ganciclovir has been reported in patients with AIDS and cytomegalovirus retinitis. 16 patients received intravenous ganciclovir 5 to 10 mg/kg/day and recombinant human GM-CSF 1 to 15 μg/kg/day. Patients received treatment for 20 days to 8 months. Ganciclovir resistance did not develop in any patient and progression of retinitis was prevented in most patients (Grossberg et al. 1989). The concomitant administration of human cytomegalovirus immune globulin and ganciclovir in patients with AIDS and cytomegalovirus retinitis did not appear to be of additional clinical benefit, with the time to disease progression being less ($p = 0.06$) than that of historical controls (Jacobsen et al. 1990).

Cytomegalovirus retinitis has also been treated successfully with ganciclovir in patients who were immunologically compromised as a result of solid organ or bone marrow transplant, leukaemia, or myelofibrosis (Buhles et al. 1988; Daikos et al. 1988; D'Alessandro et al. 1989; Erice et al. 1987; Palestine et al. 1986; Rosecan et al. 1986; Snydman 1988; Thomson & Jeffries 1989). Unlike patients with AIDS, these patients often do not require maintenance ganciclovir therapy to control disease progression as immune system recovery serves to prevent further active infection. However, in 1 patient with chronic lymphocytic leukaemia, retinitis did not respond and the cytomegalovirus isolate appeared to be ganciclovir resistant (Erice et al. 1989).

4.1.2 Intravitreal Ganciclovir Therapy

Intravitreal administration of ganciclovir for the treatment of cytomegalovirus retinitis has been evaluated exclusively in patients with AIDS. Intravitreal therapy was initiated in 42 eyes of 30 patients with AIDS and cytomegalovirus retinitis associated with factors including concomitant zidovudine therapy (8 patients), bone marrow suppression precluding intravenous ganciclovir therapy (18 patients) and/or progressive or breakthrough retinitis despite intravenous ganciclovir therapy (9 patients); the latter group continued to receive maintenance intravenous ganciclovir therapy.

Intravitreal ganciclovir 200μg to 400μg in a 50μl to 100μl volume was usually injected under topical or retrobulbar anaesthesia once or twice weekly into the treated eye(s) for up to 4 weeks initially (induction), then once weekly (maintenance). However, 1 patient received ganciclovir 2.23mg in each eye. Overall 31 eyes showed clinical improvement (usually evaluated by ophthalmoscopy) and 4 eyes stabilised, with improvements being observed within 2 to 3 weeks. As with intravenous ganciclovir therapy, ophthalmoscopic response was not always associated with an improvement in visual acuity, although the latter was observed in some patients. Relapse occurred after 2 to 5 months in 4 eyes of 3 patients receiving maintenance therapy with ganciclovir 200μg once weekly. Intravitreal ganciclovir was increased to 400μg once weekly in 1 patient and 2 patients received a second course of induction therapy (ganciclovir 200 μg/injection as 6 injections over 2 to 3 weeks); all 4 eyes responded.

Retinitis progressed in the untreated fellow eyes

Table VII. Efficacy of intravenous ganciclovir in immunologically compromised patients with severe[a] human cytomegalovirus (HCMV) pneumonia

Reference	Reason for immunological compromise	Ganciclovir therapy [mg/kg] (duration)[b]		Clinical response to initial therapy[c]	Clinical response following relapse[c]	Comments
		induction	maintenance			
Bone marrow transplant recipients						
Collaborative DHPG Treatment Study Group (1986)	BMT	10-15/day (14 days)		0/1		Patient died of respiratory failure before completing induction therapy
Emanuel et al. (1988)	BMT	10/day (14-21 days)		0/2		Died of respiratory failure within 20 days
Erice et al. (1987)	BMT	7.5/day[d] (10-20 days)	5/day	7/11	0/2	2/7 patients alive at 7 months; both had received maintenance
Milliken et al. (1989); Selby et al. (1986)	BMT	7.5/day[d] (10-20 days)	5/day (≤35 days)[d]	7/16	1/1	2 responders died of GvHD at 5 months (n=1) or fulminant pneumonitis of unknown aetiology at 6 months
Shepp et al. (1985)	BMT	7.5 or 15/day (14-17 days)		1/10		9 patients died of respiratory failure after 10 (median) days' therapy. Responder died of GvHD 72 days after pneumonia onset
Thomson & Jeffries (1989)	BMT	5-11/day (4-24 days)[d]		10/21		
Turner et al. (1986)	BMT	7.5/day (<5 days)		0/2		Died without completing induction therapy
Winston et al. (1988); Ho et al.(1989)	BMT	2.5-15/day[d] (med 19 days)	6/day, 5 days/wk	2/13[e]		
Solid organ transplant recipients						
Cantarovich et al. (1988)	RT	10/day (7-14 days)[def]		1/1		
Creasy et al. (1986)	RT[g]	10/day		1/1		Previous therapy with hyperimmune HCMV globulin was unsuccessful
Erice et al. (1987)	RT	7.5/day[d] (10-20 days)		3/3		Complete response
Harbison et al. (1988)	LT RT	7.5/day[d] (≥10 days)		3/4 2/2		1 improved patient remained HCMV culture-positive. 1 patient died on day 28 – cultures were HCMV-negative
Keay et al. (1988)	HLT HT	10/day[d] (14 days)	5-6/day on 3-7 days/wk (3-44 doses)	6/6 4/7	2/2 4/4	3 patients died before completing induction therapy
Metselaar & Weimar (1989)	RT[g]	10/day[d] (6-15 days)		4/6		Ganciclovir was withdrawn because of severe neutropenia in the 2 nonresponders. 2/3 dialysis patients responded

Table VII. Contd

Reference	Reason for immunological compromise	Ganciclovir therapy [mg/kg] (duration)[b]		Clinical response to initial therapy[c]	Clinical response following relapse[c]	Comments
		induction	maintenance			
Solid organ transplant recipients (contd)						
Nicholson et al. (1988)	RT	10/day (14 days)		4/5		1 responding patient died
Paya et al. (1988)	LT, RT[e]	7.5/day[d] (6-19 days)		8/9		
Rostoker et al. (1988)	RT	10/day (14 days)		5/5		1 patient relapsed[e]
Snydman (1988)	RT	0.5-10/day[d] (med 13 days)	30/wk (5 wks; n=1)	6/10		2 responders received HCMV immune globulin; 2 responders died of other causes; 4 nonresponders died of respiratory arrest
Stoffel et al. (1988)	RT[g]	7.5/day[d] (10-20 days) 5-11/day (4-24 days)[d]		7/8	1/1	
Thomson & Jeffries (1989)	HT LT RT		4/6 5/6 9/12			
Tucker et al. (1987)	HT	7.5/day (14-20 days)		3/3		
Turner et al. (1986)	HT RT	7.5/day (≤22 days)		1/1 1/1		1 patient died of unrelated causes
Watson et al. (1988)	HT	7.5/day[d] (10-14 days)		4/4		
Winston et al. (1988); Ho et al. (1989)	LT RT	2.5-15/day[d] (med 19 days)		2/3[e] 1/1		
Patients with acquired immune deficiency syndrome (AIDS)						
Bach et al. (1985); Bach (1986); Bach & Hedstrom (1987)	AIDS	360 mg/day (30 days; n=1) or 7.5/day (20 days)	5	3/3	1/2	1 patient refused further maintenance; 1 patient died without relapse
Buhles et al. (1988)	AIDS	7.5 or 10/day[d] (≥10 days)	5/day 2-3 days/wk or 5-6/day 5-7 days/wk	18/23	[e]	
Chachoua & Dieterich (1986)	AIDS	10/day (14 days)		5/5	[e]	'Significant' relapse rate
Collaborative DHPG Treatment Study Group (1986)	AIDS	10-15/day (14 days)		3/5		2 patients died of respiratory failure before completing induction. 3 responders died of pulmonary failure 1.5-7 weeks later
Erice et al. (1987)	AIDS	7.5/day[d] (10-20 days)	5/day	2/3		

Table continues on following page

Table VII. Contd

Reference	Reason for immunological compromise	Ganciclovir therapy [mg/kg] (duration)[b]		Clinical response to initial therapy[c]	Clinical response following relapse[c]	Comments
		induction	maintenance			
Patients with acquired immune deficiency syndrome (AIDS) [contd]						
Laskin et al. (1987a)	AIDS	3-15/day (mean 14 days)	2.1-5/day 3-7 days/wk (2-154 days)	10/14	[e]	
Laskin et al. (1987b)	AIDS	3 or 7.5/day (8-24 days)		3/4	3/3	
Masur et al. (1986)	AIDS	7.5/day (10 days)		1/1	1/1	
Winston et al. (1988); Ho et al. 1989	AIDS	2.5-15/day (med 19 days)	6/day for 5 days/wk	5/7		2 patients refused maintenance and relapsed (retinitis, colitis)
Other reasons for immunological compromise						
Collaborative DHPG Treatment Study Group (1986)	SCIDS	10-15/day (14 days)		0/1		Died of respiratory failure before completing induction therapy, aged 3 months
Erice et al. (1987)	AML (n=1) SLE (n=1)	7.5/day[d] (10-20 days)		2/2		
Keay et al. (1987)	Cancer chemotherapy	10/day (10 days)	5/day 5 days/wk (2wks)	1/1		
Turner et al. (1986)	Lymphoma	7.5/day (≤22 days)		1/1		
Winston et al. (1988); Ho et al. (1989)	Lymphoma (n=1) SLE (n=1)	2.5-15 day[d] (med 19 days)	6/day 5 days/wk	1/2		Patient with SLE did not respond
Unspecified reasons for immunological compromise[e]						
Buhles et al. (1988)	Transplant Other	7.5 or 10/day (≥10 days)	5/day 2-3 days/wk or 5-6/day 5-7 days/wk	6/10 2/3		Not specified whether BMT or SOT recipients. Underlying disease was not specified but was not AIDS
Thompson & Jeffries (1989)	Other	5-11/day (4-24 days)[d]		9/13		Not transplant recipients

a As defined by the authors - usually life-threatening.
b Induction therapy usually administered in 2 or 3 divided doses per day. Dosages are mg/kg unless otherwise stated.
c Clinical response includes partial and complete responses. Following relapse patients usually received repeat induction therapy or increased maintenance therapy.
d Dosage modified according to haematological parameters and/or renal function.
e Full details not provided.
f Authors rated disease as 'moderate' interstitial pneumonitis.
g Immunosuppressive therapy was decreased or withdrawn.

Abbreviations: BMT = bone marrow transplant; med = median; GvHD = graft *vs* host disease; RT = renal transplant; LT = liver transplant; HLT = heart-lung transplant; HT = heart transplant; SCIDS = severe combined immune deficiency syndrome; AML = acute myelogenous leukaemia; SLE = systemic lupus erythematosus; SOT = solid organ transplant.

of 4 patients with bilateral disease, whereas in 3 patients with unilateral disease retinitis did not develop in the untreated fellow eye although systemic ganciclovir was not administered (Büchi et al. 1988; Cantrill et al. 1989; Daikos et al. 1988; Harris & Mathalone 1989; Heery & Hollows 1989; Henry et al. 1987a,b; Ussery et al. 1988; Visser & Bos 1986).

4.2 Cytomegalovirus Pneumonia

Pulmonary cytomegalovirus infection in immunologically compromised patients has been associated with a poor prognosis. Development of interstitial pneumonitis in these patients may be associated with T cell cytotoxicity directed against viral and/or leucocyte antigens expressed on the surface of cytomegalovirus-infected cells in the lung (Grundy et al. 1987). Although ganciclovir monotherapy may prevent the production of cytomegalovirus virions, it does not appear to prevent the production of viral proteins, which continue to be expressed on the cell surface (section 1.3). Thus, some patients with cytomegalovirus pneumonia may appear to respond to ganciclovir therapy, becoming cytomegalovirus culture-negative, but nevertheless develop interstitial pneumonitis as a result of immune-mediated damage directed against infected cells. Bone marrow transplant recipients, particularly those with graft *vs* host disease (GvHD), appear to be especially at risk (table VII). Concomitant administration of ganciclovir with cytomegalovirus immune globulin has in some cases proved beneficial in these patients (table VIII), possibly as a result of the immunogobulin molecules binding to the expressed antigens, reducing the cytotoxic T cell response (Rook 1988). Conversely, patients with AIDS have poor cytotoxic T cell responses, and these patients appear to respond well to ganciclovir monotherapy of cytomegalovirus pneumonia (Frank & Friedman 1988).

4.2.1 Ganciclovir Monotherapy

Studies investigating ganciclovir monotherapy in immunologically compromised patients with severe cytomegalovirus pneumonia have shown consistently good clinical responses in solid organ transplant recipients and patients with AIDS. However, responses have been variable in bone marrow transplant recipients, with some studies showing little benefit while others reported a greater than 50% rate of response to ganciclovir therapy (table VII).

Although these studies involved only small numbers of patients, the results suggest that several factors affect the likelihood of a successful treatment outcome. Many patients classified as nonresponders died before completing ganciclovir induction therapy (table VII). Hence, prompt diagnosis is required (Fibbe et al. 1988), with a shortened disease course and reduced incidence of superinfection reported in renal transplant recipients in whom ganciclovir therapy was initiated relatively early (Cantarovich et al. 1988). Stoffel et al. (1988) recommended that ganciclovir therapy be initiated as soon as possible in renal transplant recipients who develop a fever of unexplained origin 1 to 3 months post-transplant. Ganciclovir has also been reported to be more effective in bone marrow transplant recipients with cytomegalovirus pneumonia when given early in infection, and it has been suggested that prophylactic ganciclovir therapy may be beneficial in these patients (section 4.6; Winston et al. 1988). A relatively high ganciclovir dosage regimen and a prolonged treatment duration have also been reported to improve patient survival and reduce relapse rate, but may be limited by toxicity (Laskin et al. 1987b; Stoffel et al. 1988).

Relapse is relatively uncommon in solid organ transplant recipients, particularly those receiving a prolonged course of induction therapy, probably in association with their relatively rapid recovery of immune function (table VII; Harbison et al. 1988; Stoffel et al. 1988), and those patients who do relapse generally respond to a further course of ganciclovir therapy. However, the immune system recovers slowly in bone marrow transplant recipients and is in decline in patients with AIDS, and it is recommended that these patients receive maintenance ganciclovir therapy as this appears to improve overall survival rates (Buhles et al. 1988; Chachoua

Table VIII. Efficacy of intravenous ganciclovir in combination with intravenous cytomegalovirus immune globulin in immunologically compromised patients with severe[a] human cytomegalovirus (HCMV) infection

Reference	Reason for immunological compromise	Site of HCMV infection	Ganciclovir [mg/kg/day] (duration)[b]	Cytomegalovirus immune globulin (mg/kg)[c]	Clinical response to therapy[d]	Comments
Bratanow et al. (1987)	BMT	Lung	6-7.5	[e]	2/4	2 partial responders died
		Lung	I; 10 (med 18 days) M; 6, 5 days/wk (med 46 days)	[e]	9/11	8 patients had a complete response[f]
		Other[e]	[e]	[e]	14/16	12 patients had a complete response[f]
Crumpacker et al. (1988)	BMT	Lung	10 (2-30 days)[g]	Prophylaxis after BMT[e]	4/7	1 responder died but was HCMV-negative at autopsy; 3 patients died of HCMV pneumonia
D'Alessandro et al. (1989)	LT[h]	Liver Lung	10 (10-14 days)	200 every other day (3 doses) then 200/wk while hospitalised	2/2 2/2	All patients had a complete response[f]
de Hemptinne et al. (1988)	LT[h]	Liver Lung	10 (11-19 days)	10 ml/kg twice weekly as prophylaxis 10 ml/kg/day treatment[i]	6/7 3/4	3 patients had hepatitis and pneumonia; 1 died although HCMV infection was controlled
Emanuel et al. (1988)	BMT	Lung	I; 7.5 (20 days)[g] M; 5, 3-5 days/wk (20 doses)	200 every 3wks as prophylaxis; 500 every other day treatment (≤18 doses)	8/10	7 patients had a complete response[f]; 1 patient died after leukaemia relapse. Ganciclovir was withdrawn in 2 neutropenic patients who also subsequently died
Hecht et al. (1988)	RT[h]	Lung	10(≤14 days)[g]	Prophylaxis[e]	1/2	1 patient died; HCMV-positive at autopsy
Reed et al. (1988a)	BMT	Lung	I; 7.5 (med 14 days) M; 5 (med 11 days)	400 on days 0,2,7; 200 on days 14,21	13/25	4 responders relapsed and died; 5 patients had a complete response[f]
Schmidt et al. (1988)	BMT	Lung	I; 10 (med 21 days) M; 5, 5 days/wk	I; 500 every other day (med 21 days) M; 500/wk	11/13	2 patients died of HCMV pneumonia; 2 responders also died

Table VIII. Contd

Reference	Reason for immuno-logical compromise	Site of HCMV infection	Ganciclovir [mg/kg/day] (duration)[b]	Cytomegalovirus immune globulin (mg/kg)[c]	Clinical response to therapy[d]	Comments
Thomson & Jeffries (1989)	BMT	Lung	5-11 (4-24 days)[g]	[e]	1/4	
	Other[e]	Lung			3/5	Not transplant recipients
Verdonck et al. (1989)	BMT	Lung	7.5 (20 days)	400 on days 0,4,8; 200 on days 12,16	3/4	1 patient died of HCMV pneumonia after 2 days of treatment; 3 responders died after HCMV cultures became negative
Wreghitt (1989)	HLT	Lung	10 (6-28 days)	1 ampoule every 7-10 days prophylactically[e]	3/3	

a As stated by the authors - usually defined as life-threatening.
b Induction therapy usually administered in 2 or 3 divided doses per day.
c mg/kg unless otherwise indicated. Some studies stated that patients received 'hyperimmune' cytomegalovirus globulin. Efficacy of each preparation may vary according to the source.
d Includes partial and complete responders.
e Full details not provided.
f Usually defined as resolution of all symptoms, ability to resume normal activities and/or long term survival.
g Dosage modified according to haematological parameters and/or renal function.
h Immunosuppressive therapy was decreased or withdrawn.
i Plasma from immunised donors.
Abbreviations: BMT = bone marrow transplant; LT = liver transplant; RT = renal transplant; I = induction therapy; M = maintenance therapy; med = median; HLT = heart-lung transplant recipients.

& Dieterich 1986; Erice et al. 1987; Laskin et al. 1987b).

Cytomegalovirus pneumonia has also been treated successfully with ganciclovir in small numbers of patients with various other causes of immunological compromise (table VII).

4.2.2 Combination Therapy with Ganciclovir and Cytomegalovirus Immune Globulin

Severe human cytomegalovirus pneumonia is often associated with a poor clinical outcome despite apparent clearing of infection. This is particularly common in bone marrow transplant recipients in whom immune function is profoundly depressed initially. Cytomegalovirus immune globulin or 'hyperimmune' cytomegalovirus globulin has been administered prophylactically or concomitantly with ganciclovir to transplant recipients in an attempt to modify the immunopathological responses thought to be associated with the development of interstitial pneumonitis (table VIII).

Ganciclovir combined with 'aggressive' cytomegalovirus immune globulin therapy appears to improve clinical outcome compared with relatively low dose prophylactic therapy. Thus, Emanuel et al. (1988) compared results in 10 patients receiving combination therapy with those of 11 historical controls consisting of similar bone marrow transplant recipients who received monotherapy with ganciclovir 5 mg/kg twice daily for 14 to 21 days (n = 2; table VII), or hyperimmune cytomegalovirus globulin (n = 5) or standard immune glob-

ulin (n = 4) 400 mg/kg/day for 10 days. All control patients died within 2 to 42 days of pneumonia onset and cytomegalovirus pneumonia was confirmed in the 9 patients who underwent autopsy. In this study the survival of patients receiving ganciclovir and hyperimmune cytomegalovirus globulin was significantly ($p = 0.001$) improved over that of the historical controls. Similarly, Reed et al. (1988a) compared patients receiving combination therapy (table VIII) with 89 similar historical controls who had received vidarabine, leucocyte interferon, vidarabine and interferon, aciclovir, aciclovir and interferon, aciclovir and vidarabine, ganciclovir alone, ganciclovir plus corticosteroids, or cytomegalovirus immune globulin alone for initial episodes of cytomegalovirus pneumonia following bone marrow transplantation, and also found that ganciclovir in combination with cytomegalovirus immune globulin significantly ($p < 0.001$) improved initial survival compared with all other treatments. This study also noted that patients surviving cytomegalovirus pneumonia following ganciclovir plus cytomegalovirus immune globulin combination therapy were significantly younger than those who did not survive (mean age 25 *vs* 37 years; $p = 0.002$).

4.3 Cytomegalovirus Gastrointestinal Disease and Hepatitis

The clinical profile and predominant distribution of gastrointestinal human cytomegalovirus infection also varies in association with the underlying immune defect. In patients with AIDS almost any part of the gastrointestinal tract may be affected, with colitis appearing to be particularly common. Oesophageal ulceration in association with cytomegalovirus infection is found most frequently in patients with AIDS (Pinching 1989), although oesophageal involvement has also been reported in limited numbers of renal (Harbison et al. 1988) and heart (Sinnott et al. 1987) transplant recipients.

Although many patients with AIDS do not have a complete response to ganciclovir therapy, cytomegalovirus disease progression is usually arrested (Erice et al. 1987). Patients not receiving ganciclovir usually have persistent infection (table IX; Buhles et al. 1988; Smith et al. 1988). Patients with AIDS who received maintenance therapy had a lower rate of relapse than those who did not (Chachoua & Dieterich 1986; Jacobsen et al. 1988c) and withdrawal of maintenance ganciclovir usually resulted in relapse (Macdonald 1987). Jacobson et al. (1988d) also reported significant ($p = 0.03$) reductions in pain and diarrhoea recurrence in patients receiving maintenance therapy immediately after induction compared with those who did not.

In the study reported by Dieterich et al. (1988), which included patients with AIDS and cytomegalovirus infection of the colon, oesophagus, stomach, small bowel, rectum and liver, no significant differences in response to ganciclovir according to the site of infection were observed. These patients had received maximum other medical treatment (for example H_2-receptor antagonists, sucralfate, antacids) for more than 6 weeks before receiving ganciclovir.

Unlike patients with AIDS, transplant recipients and those with other causes of immunological compromise generally do not require maintenance ganciclovir therapy to prevent clinical relapse of cytomegalovirus gastrointestinal or hepatic infection, and complete responses are relatively common in this patient group (table IX). Ganciclovir has been successfully used in combination with cytomegalovirus immune globulin in liver transplant recipients with cytomegalovirus hepatitis (table VIII; D'Alessandro et al. 1989; de Hemptinne et al. 1988).

4.4 CNS and Disseminated Cytomegalovirus Infection

Human cytomegalovirus CNS infection often occurs as disseminated cytomegalovirus disease, and reports on the use of ganciclovir in this indication are limited to a few small series or individual case reports. Assessment of the efficacy of ganciclovir in this setting is complicated by the difficulty of differential diagnosis of cytomegalo-

virus CNS infection, particularly in patients with AIDS where a variety of other aetiologies, including HIV encephalopathy, toxoplasmosis and cryptococcal meningitis are possible.

A relatively large number of investigators have reported using ganciclovir in varying dosage schedules in 1 or a few patients with confirmed or suspected CNS cytomegalovirus infection (for example Graveleau et al. 1989; Henderly et al. 1987; Jacobson et al. 1988a; Laskin et al. 1987a; Masdeu et al. 1988; Metselaar & Weimar 1989; Miller et al. 1988; O'Donnell et al. 1987; Snydman 1988). While improvement was reported in a few patients (Henderly et al. 1987; Metselaar & Weimar 1989; O'Donnell et al. 1987), others failed to respond and some worsened during ganciclovir administration (see, for example, Laskin et al. 1987a). Thus, while in the absence of other more effective treatments further study may be merited to try and improve the response to ganciclovir by identifying optimum dosage schedules, at this stage its use in CNS cytomegalovirus infection is not established.

In a few heart (Keay et al. 1988) or liver (Elenitsas & Cohen 1988; Stein et al. 1988) transplant recipients receiving up to 10 mg/kg/day of ganciclovir the outcome was mixed, and clear conclusions are not possible. However, Kotler et al. (1986) retrospectively analysed results from 18 patients with AIDS and disseminated cytomegalovirus infection who received ganciclovir 2.5 mg/kg 3 times daily for 2 weeks then 6 mg/kg/day 5 days/week (n = 12) increased to 5 mg/kg twice daily (n = 20), and in some cases nutritional support. A similar group of 11 historical controls who received extensive support therapy, including parenteral nutritional support in most cases (n = 8) were analysed for comparison. Patients who received ganciclovir had a significantly longer mean survival time compared with controls (162 *vs* 53 days; $p < 0.005$), and a greater duration of survival as measured by life-table analysis ($p < 0.001$). Progressive cytomegalovirus infection was not implicated in the death of any ganciclovir recipient (n = 12) and cytomegalovirus infection was rediagnosed within 2 months in 6 patients who discontinued ganciclovir therapy.

4.5 Prophylactic Ganciclovir Therapy

Early diagnosis and treatment of human cytomegalovirus infection appears to improve clinical outcome, particularly in bone marrow transplant recipients (section 4.2.1). This has led to speculation that prophylactic ganciclovir therapy may be useful, especially in high-risk patient groups. This hypothesis is being tested in a double-blind placebo-controlled study in cytomegalovirus-seropositive allogeneic bone marrow transplant recipients. Patients receive intravenous ganciclovir 2.5 mg/kg 8-hourly for 1 week immediately before donor marrow infusion, then 6 mg/kg/day 5 days/week from when neutrophil count reaches 500 cells/mm^3 to day 120 after transplant. Although the efficacy of prophylactic ganciclovir has not yet been determined, it does not appear to adversely affect marrow engraftment (Winston et al. 1988).

5. Adverse Effects

Several factors confound the evaluation of adverse effects related to ganciclovir therapy. The underlying cause of immunological compromise may produce symptomatic effects. Many patients receive multiple concomitant medications and/or have other concomitant infections, and attributing an adverse event to a single cause may be difficult. Thus, the best way to evaluate the incidence and nature of adverse effects associated with ganciclovir is to study large numbers of patients in placebo-controlled trials. Unfortunately results from such studies are as yet unavailable and most data are from uncontrolled trials and case reports. The proportion of patients treated with ganciclovir in whom therapy is subsequently interrupted or withdrawn because of adverse effects is estimated at 32% (data on file, Syntex), although in many patients reintroduction of ganciclovir or use of a lower dosage regimen is later successful.

5.1 Haematological Effects

Following an intravenous infusion of 5 mg/kg, peak plasma ganciclovir levels exceed the IC_{50} for

Table IX. Efficacy of intravenous ganciclovir in immunologically compromised patients with severe[a] gastrointestinal and/or hepatic human cytomegalovirus (HCMV) infection

References	Site of HCMV infection	Ganciclovir [mg/kg/day] (duration)[b]	Initial clinical response[c] (response after relapse)[d]	Comments
Patients with acquired immune deficiency syndrome (AIDS)				
Buhles et al. (1988); Chachoua & Dieterich (1986); Collaborative DHPG Treatment Study Group (1986); Dieterich et al. (1988); Erice et al. (1987); Ho et al. (1989);	Upper GI	I; 7.5 or 10 (14 days) M; 5, 5 days/wk	27/34 (1/1)	Patients receiving M had a lower relapse rate than those not receiving M. Most relapsing patients responded to repeat I therapy. One study found no difference in response according to disease site
	Lower GI	I; 7.5 or 10 (10-20 days) M; 5, 5 days/wk	68/82 (2/2)	
Jacobson et al. (1988d); Laskin et al. (1987a, 1987b); Lim et al. (1988); Macdonald (1987); Masur et al. (1986); O'Donnell et al. (1987)	GI[e]	I; 10 (14 days) M[e]	24/28 (1/11)	
Smith et al. (1988); Winston et al. (1988)	GI[e]	None	2/17	Most control patients had persistent infection. Response rate was significantly lower than that of patients receiving ganciclovir
Bach & Hedstrom (1987); Dieterich et al (1988); Erice et al. (1987)	Liver	I; 7.5 or 10 (10-20 days) M; 5	5/6	
Bone marrow transplant recipients				
Erice et al. (1987); Reed et al. (1988b)	GI[e]	3 or 7.5 (10-20 days)	14/18	No clinical relapse; 2 patients had pulmonary infiltrates 21 days after therapy; 1 died of HCMV pneumonia; 2 patients had no evidence of HCMV infection but persistent GI symptoms - possibly GvHD
Heart transplant recipients				
Keay et al. (1988); Sinnott et al. (1987)	Upper GI	5-10 (≥10 days)	4/4	No clinical relapses
	Lower GI	7.5-10 (≥14 days)	1/2	1 patient died on day 8 of therapy; 1 patient died 8 days after therapy but death was not attributed to HCMV infection
Liver transplant recipients				
Erice et al. (1987); Harbison et al. (1988); Ho et al. 1989; Paya et al. (1988); Winston et al. (1988)	Liver	7.5 (6-30 days)	14/19	No clinical relapses; 1 non-responder died on day 6 secondary to erosive duodenitis - no HCMV-duodenitis at autopsy; 1 non-responder died on day 10.
Renal transplant recipients				
Cantarovich et al. (1988); Erice et al. (1987);	Upper GI	7.5 or 10 (7-30 days)	5/5	No clinical relapses although 2 patients died of other causes
Harbison et al. (1988); Paya et al. (1988); Rostoker et al. (1988)	Lower GI	7.5 or 10 (6-19 days)	3/3	No clinical relapses

Table IX. Contd

References	Site of HCMV infection	Ganciclovir [mg/kg/day] (duration)[b]	Initial clinical response[c] (response after relapse)[d]	Comments
Renal transplant recipients (contd)				
Metselaar & Weimar (1989)	GI[e]	1.5 or 10 (8 or 15 days)	1/2	1 patient with concomitant HCMV pneumonitis died after ganciclovir was withdrawn because of severe neutropenia
Cantarovich et al. (1988); Metselaar & Weimar (1989); Paya et al. (1988)	Liver	7.5 or 10 (6-19 days)	14/14	No clinical relapses
Other immunologically compromised patients[e]				
Buhles et al. (1988)	Lower GI	7.5 or 10 (≥10 days)	0/1	Transplant recipient
	Lower GI	7.5 or 10 (≥10 days)	2/2	
Topiel et al. (1986)	Lower GI/liver	7.5 (3 wks)	1/1	Patient with Crohn's disease receiving steroids. No clinical relapse

a As defined by the authors - usually life-threatening.
b Dosage scheduled to be received by most patients; usually adjusted according to haematological and/or renal parameters.
c Patients who had nonprogression/stabilisation, partial or complete response of HCMV disease.
d Where stated.
e Not fully defined.
Abbreviations: GI = gastrointestinal tract; I = induction therapy; M = maintenance therapy; GvHD = graft *vs* host disease.

growth inhibition of human bone marrow colony-forming cells *in vitro* (section 2; section 3; Henderson 1989; Matthews & Boehme 1988). Thus, some degree of bone marrow depression can be expected to occur in patients receiving ganciclovir therapy.

Neutropenia is the most frequent adverse effect associated with ganciclovir therapy and is usually defined as a greater than 50% decrease in absolute neutrophil count from baseline or less than 1000 neutrophils/μl. In several studies it has been the only adverse effect attributable to ganciclovir (see for example Harbison et al. 1988; Ho et al. 1989; Kotler et al. 1986; Reed et al. 1988a). Development of neutropenia appears to be associated with the total dose of ganciclovir administered, usually occurring before a total cumulative dose of 200 mg/kg has been given, although it may occur at any time during induction or maintenance therapy. The overall incidence of neutropenia in patients receiving ganciclovir is about 40% (Syntex, data on file), with AIDS patients appearing more likely to develop neutropenia than other ganciclovir recipients (Ho et al. 1989; Syntex, data on file). Occurrence of neutropenia does not appear to be predicted by pretreatment absolute neutrophil count or ganciclovir dosage regimen (Buhles et al. 1988; Holland et al 1987; Syntex, data on file). Although the incidence of neutropenia has been slightly reduced in patients receiving ganciclovir 2.5 mg/kg 3 times daily compared with those receiving 5 mg/kg twice daily in some studies (see for example Winston et al. 1988), this probably reflects the higher cumulative dosage with time in the latter patients. Paradoxically, in some patients a rise in neutrophil counts has been observed during ganciclovir therapy, including patients considered mildly neutropenic before treatment (Reed et al. 1988b; Stoffel et al. 1988; Verdonck et al. 1989). However, intravenous ganciclovir administration is not rec-

ommended if absolute neutrophil count is below 500/μl (Syntex, data on file).

Increased risk of bacterial infection is an important clinical consequence of neutropenia in general; however, the incidence of bacterial infection associated with ganciclovir-induced neutropenia is difficult to determine as these patients are often already severely immunocompromised. There have been several reports of patients developing superinfections while neutropenic as a result of ganciclovir treatment (see for example Buhles et al. 1988; Reed et al. 1988b), although other investigators have not found an association between leucopenia and bacterial sepsis or other opportunistic infections (Dieterich et al. 1988).

Thrombocytopenia, usually defined as a platelet count below 50 000/μl, occurs in about 20% of ganciclovir recipients overall (Syntex, data on file) but more frequently where AIDS is not the underlying cause for being immunocompromised (Buhles et al. 1988; Syntex, data on file). In addition, patients with initial platelet counts below 100 000/μl appear to have an increased risk of developing thrombocytopenia during ganciclovir therapy (Syntex, data on file), although in some studies patients who initially had mild thrombocytopenia had an increase in platelet counts during ganciclovir treatment (Harbison et al. 1988; Snydman 1988). Upper gastrointestinal bleeding developed in 1 patient in whom platelet counts had decreased from 337 000 to 1000/μl following 6 days' treatment with ganciclovir 2.5 mg/kg 3 times daily for cytomegalovirus retinitis. Despite stopping ganciclovir and whole blood and platelet transfusions, the patient remained thrombocytopenic, developed vitreous and intracranial haemorrhages, and subsequently died. It was suggested that acid-fast bacilli, demonstrated in the bone marrow prior to ganciclovir therapy, may have sensitised the patient to thrombocytopenia (Robinson et al. 1989).

Other haematological adverse effects of ganciclovir therapy include anaemia, which is estimated to occur in about 2% of patients (Bailleul 1988; Buhles et al. 1988; Jacobson et al. 1988c; Syntex, data on file) and eosinophilia which has been reported in several patients (Buhles et al. 1988; Collaborative DHPG Treatment Study Group 1986). Pure red cell aplasia has been observed in 1 bone marrow transplant recipient receiving ganciclovir (Emanuel et al. 1988) and haemolysis has been reported in 2 other patients (Thomson & Jeffries 1989). Leucopenia also occurs in some patients although this is usually mild and may reflect reduced numbers of specific cell populations (for example, neutrophils) [Cantarovich et al. 1988; Dieterich et al. 1988; Harbison et al. 1988; Laskin et al. 1987a, b; Thomson & Jeffries 1989; Watson et al. 1988].

In general, the adverse haematological effects of ganciclovir are rapidly reversible following treatment withdrawal, with evidence of recovery usually observed within 3 to 7 days (Syntex, data on file). However, in addition to the patient with severe thrombocytopenia described above, irreversible neutropenia has been described in a patient who subsequently died of sepsis (Buhles et al. 1988). Withdrawal of ganciclovir is usually associated with progression of cytomegalovirus disease, so in some patients with haematological adverse effects discontinuation of concomitant myelotoxic drugs (for example azathioprine; see Nicholson et al. 1988), or in patients with cytomegalovirus retinitis switching to intravitreal ganciclovir administration (section 4.1.2), has been favoured as an alternative to withdrawal. In addition, recombinant human GM-CSF has been administered concomitantly with ganciclovir in some patients in an attempt to modify development of neutropenia (section 4.1.1; Fouillard et al. 1989).

5.2 Other Adverse Effects

There have been numerous reports of other adverse effects in patients receiving ganciclovir therapy, although the establishment of a clear causative relationship is usually difficult.

Adverse events involving the CNS have been reported in about 5% of patients (Syntex, data on file), and have included confusion, seizures, abnormal thinking, psychosis, hallucinations, mental status changes, nightmares, anxiety, tremor, dysaesthesia, ataxia, coma, headache and somnolence

(Buhles et al. 1988; Chachoua & Dieterich 1986; Collaborative DHPG Treatment Study Group 1986; Dieterich et al. 1988; Jabs et al. 1987; Keay et al. 1987, 1988; Orellana et al. 1987; Snydman 1988; Thomson & Jeffries 1989; Syntex, data on file). Several of these patients had concomitant toxoplasmosis and 1 patient was hypoxic prior to ganciclovir infusion (Chachoua & Dieterich 1986; Dieterich et al. 1988; Keay et al. 1987).

Fever, rash and abnormal liver function values are each reported to occur in about 2% of ganciclovir recipients (Syntex, data on file). Retinal detachment has been reported in patients with cytomegalovirus retinitis receiving ganciclovir therapy but this could be attributable to retinal scarring in some cases (Holland et al. 1987; Rosecan et al. 1986; Ussery et al. 1988; Syntex, data on file), with spontaneous reattachment reported in 1 patient after ganciclovir withdrawal (Orellana et al. 1987). Other reported adverse effects which may or may not be associated with ganciclovir therapy and occur in 1% or fewer of patients include chills, oedema, infection, malaise, arrhythmia, changes in blood pressure, nausea, vomiting, anorexia, diarrhoea, dyspnoea, decreased blood glucose, alopecia, decreased kidney function and inflammation, pain or phlebitis at the infusion site (Buhles et al. 1988; Emanuel et al. 1988; Keay et al. 1987; 1988; Shepp et al. 1985; Watson et al. 1988; Syntex, data on file).

Adverse effects reported in patients receiving intravitreal ganciclovir therapy include local foreign body sensation, conjunctival haemorrhage or mattering, mild conjunctival scarring, scleral induration, bacterial endophthalmitis (usually staphylococcal) and retinal detachment (Büchi et al. 1988; Cantrill et al. 1989; Harris & Mathalone 1989; Heinemann 1989; Ussery et al. 1988). Although not observed clinically, animal data indicate ganciclovir may inhibit spermatogenesis and fertility (Syntex, data on file). While no significant changes in serum gonadotropic hormone levels were observed in 32 men during ganciclovir therapy (Dieterich et al. 1988), caution is recommended in this regard (section 7).

6. Drug Interactions

Generalised seizures have been noted in 6 patients receiving imipenem/cilastatin with ganciclovir and potential risks and benefits should be weighed in patients in whom this combination is proposed (Syntex, data on file). Zidovudine and ganciclovir have overlapping toxicity profiles with respect to adverse haematological effects and concomitant treatment with recommended dosages of these agents is not advocated by the manufacturers – pancytopenia has been noted in 1 patient receiving oral zidovudine and intravenous ganciclovir in combination, with the 2 drugs exhibiting additive or synergistic myelosuppressive effects (Jacobson et al. 1988a). Similarly, it is not recommended that drugs such as dapsone, pentamidine, flucytosine, vincristine, doxorubicin, amphotericin B, trimethoprim/sulpha combinations or other nucleoside analogues, which inhibit the replication of rapidly dividing cell populations, including bone marrow, spermatogonia, and cutaneous and gastrointestinal germinal layers, be administered concomitantly with ganciclovir unless potential benefits outweigh the risks. Finally, drugs such as probenecid, which inhibit renal tubular secretion or resorption may reduce the renal clearance of ganciclovir resulting in elevated plasma levels (Syntex, data on file).

7. Dosage and Administration

In immunocompromised patients with cytomegalovirus infection early diagnosis and prompt initiation of therapy may improve the response to ganciclovir. Ganciclovir should be administered as a 1-hour intravenous infusion; rapid or bolus injection may result in excessive plasma concentrations causing increased toxicity or nephrotoxicity as a result of drug deposition, whereas subcutaneous or intramuscular administration may result in tissue irritation because of the high pH ($\approx$ 11) of the ganciclovir solution. In patients with normal renal function ganciclovir 5 mg/kg every 12 hours or 2.5 mg/kg every 8 hours, for 14 to 21 days is recommended initially, with maintenance regi-

Table X. Adjustment of intravenous ganciclovir dosage regimen during induction therapy according to creatinine clearance (manufacturer's recommendations)

Creatinine clearance[a] (ml/1.73m^2/min)	Ganciclovir dose (mg/kg)	Dose interval (hours)
≥80	5.0	12
50-79	2.5	12
25-49	2.5	24
<25	1.25	24

a Creatinine clearance for males = ([140 − age (yrs)] [bodyweight (kg)] × 1.73/body surface area [m^2])/(72) [serum creatinine (mg/dl)]. Creatinine clearance for females = 0.85 × male value.

mens of 5 mg/kg/day, or 6 mg/kg/day 5 days/week. Patients who experience progression while receiving maintenance therapy can be retreated with the induction regimen. Indefinite maintenance therapy is usually required in patients with AIDS, whereas bone marrow transplant recipients may require ganciclovir maintenance therapy for a year or more (until immune system reconstitution) to prevent disease progression or recurrence.

In patients with renal impairment, ganciclovir dosage regimens should be adjusted according to creatinine clearance (table X). In general, renal function should be monitored at least fortnightly in ganciclovir recipients. However, Metselaar and Weimar (1989) suggest that rather than reducing the dosage in patients with renal impairment, the dose interval should be prolonged, as the currently recommended reductions may result in inadequate peak ganciclovir concentrations. Ganciclovir is removed during haemodialysis and has been successfully used in such patients (section 3.4; Metselaar & Weimar 1989).

Haematological monitoring should be performed frequently during therapy and ganciclovir should be withheld if neutrophil count falls below 500/μl or platelet count falls below 25 000/μl. Ganciclovir should be used during pregnancy only if expected benefit outweighs the potential risk to the fetus and it is recommended that nursing be discontinued until at least 72 hours after the last dose. Because of the probability of carcinogenicity and reproductive toxicity, patients of reproductive age should practise effective contraception during treatment, and in men for 90 days after completing therapy.

Intravitreal ganciclovir administration remains largely experimental although results have been promising. 200 to 400μg once or twice weekly for 3 weeks during induction therapy, then once weekly during maintenance were the most common dosages studied (section 4.1.2).

8. Place of Ganciclovir in Therapy

Ganciclovir should be considered a first-line therapy in immunocompromised patients with life- or sight-threatening cytomegalovirus infection. Within this context ganciclovir has generally proved effective, although the degree of response varies according to disease site and the underlying aetiology of immunocompromise, and efficacy is not well established in some indications (CNS infections). Patients with cytomegalovirus pneumonia, particularly bone marrow transplant recipients, appear to benefit from the concomitant administration of ganciclovir and cytomegalovirus immune globulin, with a reduction in the incidence and severity of interstitial pneumonitis which may occur despite apparent virological cure. Following treatment of an acute infection, maintenance therapy may be required (especially in AIDS patients and bone marrow recipients) to maintain viral suppression, as ganciclovir (like other antiviral drugs) does not eradicate latent viral infection.

Close patient monitoring is essential to reduce the incidence of haematological toxicity, which is a limiting factor in ganciclovir therapy. Furthermore, the long term effects of prolonged ganciclovir administration have not been fully determined. These factors currently preclude the use of ganciclovir in less severe infection, congenital or neonatal disease, or cytomegalovirus infection in non-immunocompromised patients. However, preliminary results suggest concomitant use of haemopoietic growth factors may modify the toxicity profile of ganciclovir, possibly permitting wider clinical application in the future.

Prospective comparative studies of ganciclovir and other antiviral agents have not been reported, but until recently other treatments for cytomegalovirus infections in immunocompromised patients met with minimal success (Reed et al. 1988a). However, foscarnet has recently been found to be useful in treating cytomegalovirus retinitis in AIDS patients. Although it may cause other adverse effects, it does not appear to produce significant myelosuppression which may offer advantages in AIDS patients receiving zidovudine (reviewed in Jacobson & Mills 1988). Thus, comparative studies of ganciclovir and foscarnet will be awaited with interest.

In conclusion, ganciclovir has a firmly established role in the treatment of severe cytomegalovirus infections in immunocompromised patients although trials comparing or combining ganciclovir with other antiviral agents are awaited to further define its place in therapy.

References

Agut H, Huraux J-M, Collandre H, Montagnier L. Susceptibility of human herpesvirus 6 to acyclovir and ganciclovir (PD). Lancet 2: 626, 1989

Appelbaum FR, Meyers JD, Deeg HJ, Graham T, Schuening F, et al. Toxicity trial of prophylactic 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine (ganciclovir) after marrow transplantation in dogs. Antimicrobial Agents and Chemotherapy 32: 271-273, 1988

Ashton WT, Karkas JD, Field AK, Tolman RL. Activation by thymidine kinase and potent antiherpetic activity of 2'-nor-2'-deoxyguanosine (2'NDG). Biochemical and Biophysical Research Communications 108: 1716-1721, 1982

Baba M, Konno K, Shigeta S, De Clercq E. Inhibitory effects of selected antiviral compounds on newly isolated clinical varicella-zoster virus strains. Tohoku Journal of Experimental Medicine 148: 275-283, 1986

Bach MC. Breakthrough of cytomegalovirus infection despite 9-(1,3-dihydroxy-2-propoxymethyl)guanine therapy. Annals of Internal Medicine 104: 587, 1986

Bach MC, Bagwell SP, Knapp NP, Davis KM, Hedstrom PS. 9-(1,3-dihydroxy-2-propoxymethyl)guanine for cytomegalovirus infections in patients with the acquired immunodeficiency syndrome. Annals of Internal Medicine 103: 381-382, 1985

Bach MC, Hedstrom PS. CMV retinitis treated with ganciclovir [9(1,3-dihydroxy-2-propoxymethyl)guanine] in patients with AIDS. Annals of Ophthalmology 19: 369-375, 1987

Bailleul F. Ganciclovir et rétinites a cytomégalovirus au cours du sida: résultats chez 334 patients. Médecine et Maladies Infectieuses 18 (Suppl.): 783, 1988

Biron KK, Fyfe JA, Stanat SC, Leslie LK, Sorrell JB, et al. A human cytomegalovirus mutant resistant to the nucleoside analog 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}guanine (BW B759U) induces reduced levels of BW B759U triphosphate. Proceedings of the National Academy of the Sciences of the United States of America 83: 8769-8773, 1986

Biron KK, Stanat SC, Sorrell JB, Fyfe JA, Keller PM, et al. Metabolic activation of the nucleoside analog 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}guanine in human diploid fibroblasts infected with human cytomegalovirus. Proceedings of the National Academy of the Sciences of the United States of America 82: 2473-2477, 1985

Boehme RE. Phosphorylation of the antiviral precursor 9-(1,3-dihydroxy-2-propoxymethyl)guanine monophosphate by guanylate kinase isozymes. Journal of Biological Chemistry 259: 12346-12349, 1984

Bowden RA, Digel J, Reed EC, Meyers JD. Immunosuppressive effects of ganciclovir on in vitro lymphocyte responses. Journal of Infectious Diseases 156: 899-903, 1987

Bratanow N, Ash RC, Turner P, Smith R, Chitambar C, et al. The use of 9(1,3-dihydroxy-2-propoxymethyl)guanine (ganciclovir, DHPG) and intravenous immunoglobin (IVIG) in the treatment of serious cytomegalovirus (CMV) infections in thirty-one allogeneic bone marrow transplant (BMT) patients. Abstract. Blood 70 (Suppl. 1): 302a, 1987

Büchi ER, Fitting PL, Michel AE. Long-term intravitreal ganciclovir for cytomegalovirus retinitis in a patient with AIDS Correspondence. Archives of Ophthalmology 106: 1349-1350, 1988

Buhles WC, Mastre Jr BJ, Tinker AJ. Ganciclovir treatment of life- or sight-threatening cytomegalovirus infection: experience in 314 immunocompromised patients. Reviews of Infectious Diseases 10 (Suppl. 3): S495-S506, 1988

Cantarovich M, Hiesse C, Lantz O, Fassi-Fihri S, Charpentier B, et al. Treatment of cytomegalovirus infections in renal transplant recipients with 9-(1,3-dihydroxy-2-propoxymethyl) guanine. Transplantation 45: 1139-1141, 1988

Cantrill HL, Henry K, Melroe H, Knobloch WH, Ramsay RC, et al. Treatment of cytomegalovirus retinitis with intravitreal ganciclovir. Long-term results. Ophthalmology 96: 367-374, 1989

Chachoua A, Dieterich DT. 9-1,3 dihydroxy-2 propoxymethyl guanine in patients with AIDS and CMV infections. Abstract. Clinical Research 34: 514a, 1986

Cheng Y-c, Grill SP, Dutschman GE, Frank KB, Chiou J-F, et al. Effects of 9-(1,3-dihydroxy-2-propoxymethyl)guanine, a new antiherpesvirus compound, on synthesis of macromolecules in herpes simplex virus-infected cells. Antimicrobial Agents and Chemotherapy 26: 283-288, 1984

Cheng Y-c, Grill SP, Dutschman GE, Nakayama K, Bastow KF. Metabolism of 9-(1,3-dihydroxy-2-propoxymethyl)guanine, a new anti-herpes virus compound, in herpes simplex virus-infected cells. Journal of Biological Chemistry 258: 12460-12464, 1983a

Cheng Y-c, Huang E-S, Lin J-c, Mar E-c, Pagano JS, et al. Unique spectrum of activity of 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine against herpesviruses *in vitro* and its mode of action against herpes simplex virus type 1. Proceedings of the National Academy of the Sciences of the United States of America 80: 2767-2770, 1983b

Chun Y-S, Park N-H. Effect of ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl)guanine] on viral DNA and protein synthesis in cells infected with herpes simplex virus. Antimicrobial Agents and Chemotherapy 31: 349-351, 1987

Coen DM, Fleming Jr HE, Leslie LK, Retondo MJ. Sensitivity of arabinosyladenine-resistant mutants of herpes simplex virus to other antiviral drugs and mapping of drug hypersensitivity mutations to the DNA polymerase locus. Journal of Virology 53: 477-488, 1985

Cole NL, Balfour Jr HH. In vitro susceptibility of cytomegalovirus isolates from immunocompromised patients to acyclovir and ganciclovir. Diagnostic Microbiology and Infectious Disease 6: 255-261, 1987

Collaborative DHPG Treatment Study Group. Treatment of se-

rious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl) guanine in patients with AIDS and other immunodeficiencies. New England Journal of Medicine 314: 1986

Collins P, Oliver NM. Comparison of the in vitro and in vivo antiherpes virus activities of the acyclic nucleosides, acyclovir (Zovirax) and 9-[(2-hydroxy-1-hydroxymethylethoxy) methyl] guanine (BWB759U). Antiviral Research 5: 145-156, 1985

Creasy TS, Flower AJE, Veitch PS. Life-threatening cytomegalovirus infection treated with dihydropropoxymethylguanine. Correspondence. Lancet 1: 675, 1986

Crumpacker C, Marlowe S, Zhang JL, Abrams S, Watkins P, et al. Treatment of cytomegalovirus pneumonia. Reviews of Infectious Disease 10 (Suppl. 3): S538-S546, 1988

Daikos GL, Pulido J, Kathpalia SB, Jackson GG. Intravenous and intraocular ganciclovir for CMV retinitis in patients with AIDS or chemotherapeutic immunosuppression. British Journal of Ophthalmology 72: 521-524, 1988

D'Alessandro AM, Pirsch JD, Stratta RJ, Sollinger HW, Kalayoglu M, et al. Successful treatment of severe cytomegalovirus infections with ganciclovir and CMV hyperimmune globulin in liver transplant recipients. Transplantation Proceedings 21: 3560-3561, 1989

Dankner WM, Spector SA. Determination of antiviral activity of ganciclovir (DHPG) and antiretroviral agents against human cytomegalovirus (HCMV) using a novel DNA-DNA hybridization assay. Abstract. Antiviral Research 9: 114, 1988

Davies ME, Bondi JV, Tolman RL, Field AK. Efficacy of 2′-nor-2′-deoxyguanosine treatment of orofacial HSV-1 infection in mice. Abstract. American Society for Microbiology 290, 1983

Davies, M-E M, Bondi JV, Field AK. Efficacy of 2′-nor-2′-deoxyguanosine treatment for orofacial herpes simplex virus type 1 skin infections in mice. Antimicrobial Agents and Chemotherapy 25: 238-241, 1984

Davies M-E M, Bondi JV, Grabowski I, Schofield TL, Field AK. 2′-nor-2′-deoxyguanosine is an effective therapeutic agent for treatment of experimental herpes keratitis. Antiviral Research 7: 119-125, 1987

Debs RJ, Montgomery AB, Brunette EN, DeBruin M, Shanley JD. Aerosol administration of antiviral agents to treat lung infection due to murine cytomegalovirus. Journal of Infectious Diseases 157: 327-331, 1988

de Hemptinne B, Lamy ME, Salizzoni M, Cornu C, Mostin J, et al. Successful treatment of cytomegalovirus disease with 9-(1,3-dihydroxy-2-propoxymethyl guanine). Transplantation Proceedings 20 (Suppl. 1): 652-655, 1988

De Miranda P, Burnette T, Cederberg D, Blum MR, Brodie HR, et al. Absorption and pharmacokinetics of the antiviral 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (BW B759U) in humans. Abstract. Abstracts of the 1986 ICAAC 200, 1986

Derse D, Cheng Y-C, Furman PA, St. Clair MH, Elion GB. Inhibition of purified human and herpes simplex virus-induced DNA polymerases by 9-(2-hydroxyethoxymethyl)guanine triphosphate. Journal of Biological Chemistry 256: 11447-11451, 1981

Dieterich DT, Chachoua A, Lafleur F, Worrell C. Ganciclovir treatment of gastrointestinal infections caused by cytomegalovirus in patients with AIDS. Reviews of Infectious Diseases 10 (Suppl. 3): S532-S537, 1988

Duke AE, Smee DF, Chernow M, Boehme R, Matthews TR. In vitro and in vivo activities of phosphate derivatives of 9-(1,3-dihydroxy-2-propoxymethyl)-guanine against cytomegaloviruses. Antiviral Research 6: 299-308, 1986

Ebihara K, Takahashi K, Yagisawa T, Yamaguchi H, Ota K, et al. Ganciclovir. Cytomegalovirus nephropathy. Kansenshogaku Zasshi 63: 644-648, 1989

Elenitsas R, Cohen BA. Cutaneous cytomegalovirus in a liver transplant patient. Transplantation Proceedings 20 (Suppl. 1): 656-658, 1988

Emanuel D, Cunningham I, Jules-Elysee K, Brochstein JA, Kernan NA, et al. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. Annals of Internal Medicine 109: 777-782, 1988

Eppstein DA, Marsh YV. Potent synergistic inhibition of herpes simplex virus-2 by 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine in combination with recombinant interferons. Biochemical and Biophysical Research Communications 120: 66-73, 1984

Erice A. Ganciclovir (GCV) resistant strains of cytomegalovirus (CMV) in GCV-treated patients with AIDS. IV International Conference on AIDS, Stockholm, Sweden, Jun 12-16 1988, Abstract

Erice A, Chou S, Biron KK, Stanat SC, Balfour Jr HH, et al. Progressive disease due to ganciclovir-resistant cytomegalovirus in immunocompromised patients. New England Journal of Medicine 320: 289-293, 1989

Erice A, Jordan C, Chace BA, Fletcher C, Chinnock BJ, et al. Ganciclovir treatment of cytomegalovirus disease in transplant recipients and other immunocompromised hosts. Journal of the American Medical Association 257: 3082-3087, 1987

Estes JE, Huang E-S. Stimulation of cellular thymidine kinase by human cytomegalovirus. Journal of Virology 24: 13-21, 1977

Fan-Havard P, Nahata MC, Brady MT. Ganciclovir: a review of pharmacology, therapeutic efficacy and potential use for treatment of congenital cytomegalovirus infections. Journal of Clinical Pharmacy and Therapeutics 14: 329-340, 1989

Felsenstein D, D'Amico DJ, Hirsch MS, Neumeyer DA, Cederberg DM, et al. Treatment of cytomegalovirus retinitis with 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine. Annals of Internal Medicine 103: 377-380, 1985

Fibbe WE, Zwaan FE, Richel DJ, Guiot HFL, Vosts W, et al. Reduction of the incidence of CMV-related pneumonitis by a modified conditioning regimen and early treatment with DHPG. Bone Marrow Transplantation 3 (Suppl. 1): 263, 1988

Field AK, Davies ME, DeWitt C, Perry HC, Liou R, et al. 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}guanine: a selective inhibitor of herpes group virus replication. Proceedings of the National Academy of the Sciences of the United States of America 80: 4139-4143, 1983

Field HJ, Anderson JR, Efstathiou S. A quantitative study of the effects of several nucleoside analogues on established herpes encephalitis in mice. Journal of General Virology 65: 707-719, 1984

Fletcher C, Sawchuk R, Chinnock B, de Miranda P, Balfour Jr HH. Human pharmacokinetics of the antiviral drug DHPG. Clinical Pharmacology and Therapeutics 1: 281-286, 1986

Fong CKY, Cohen SD, McCormick S, Hsiung GD. Antiviral effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine against cytomegalovirus infection in a guinea pig model. Antiviral Research 7: 11-23, 1987

Fouillard L, Gorin NC, Laporte JPh, Eugene-Jolchine I, Isnard F, et al. GM-CSF and ganciclovir for cytomegalovirus infection after autologous bone-marrow transplantation. Correspondence. Lancet 2: 1273, 1989

Frank I, Friedman HM. Progress in the treatment of cytomegalovirus pneumonia. Annals of Internal Medicine 109: 769-771, 1988

Frank KB, Chiou J-F, Cheng Y-c. Interaction of herpes simplex virus-induced DNA polymerase with 9-(1,3-dihyroxy-2-propoxymethyl)guanine triphosphate. Journal of Biological Chemistry 259: 1566-1569, 1984

Fraser-Smith EB, Eppstein DA, Marsh YV, Matthews TR. Comparison of synergistic combinations of 9-(1,3-dihydroxy-2-propoxymethyl)guanine and alpha, beta, or gamma interferon against Herpes simplex virus type 2 both in vivo and in vitro. Abstracts of the 1984 ICAA 300, 1984a

Fraser-Smith EB, Eppstein DA, Marsh YV, Matthews TR. Enhanced efficacy of the acyclic nucleoside 9-(1,3-dihydroxy-2-

propoxymethyl)guanine in combination with alpha-interferon against herpes simplex virus type 2 in mice. Antimicrobial Agents and Chemotherapy 26: 937-938, 1984b

Fraser-Smith EB, Eppstein DA, Marsh YV, Matthews TR. Enhanced efficacy of the acyclic nucleoside 9-(1,3-dihydroxy-2-propoxymethyl)guanine in combination with gamma interferon against herpes simplex virus type 2 in mice. Antiviral Research 5: 137-144, 1985

Fraser-Smith EB, Smee DF, Matthews TR. Efficacy of the acyclic nucleoside 9-(1,3-dihydroxy-2-propoxymethyl)guanine against primary and recrudescent genital herpes simplex virus type 2 infections in guinea pigs. Antimicrobial Agents and Chemotherapy 24: 883-887, 1983

Freitas VR, Smee DF, Chernow M, Boehme R, Matthews TR. Activity of 9-(1,3-dihydroxy-2-propoxymethyl)guanine compared with that of acyclovir against human, monkey, and roden cytomegalovirus. Antimicrobial Agents and Chemotherapy 28: 240-245, 1985

Gadler H. Nucleic and hybridization for measurement of effects of antiviral compounds on human cytomegalovirus DNA replication. Antimicrobial Agents and Chemotherapy 24: 370-374, 1983

Germershausen J, Bostedor R, Field AK, Perry H, Liou R, et al. A comparison of the antiviral agents 2'-nor-2'-deoxyguanosine and acyclovir: uptake and phosphorylation in tissue culture and kinetics of in vitro inhibition of viral and cellular DNA polymerases by their respective triphosphates. Biochemical and Biophysical Research Communications 116: 360-367, 1983

Graveleau Ph, Perol R, Chapman A. Regression of cauda equina syndrome in AIDS patient being treated with ganciclovir. Correspondence. Lancet 2: 511-512, 1989

Grossberg HS, Bonnem EM, Buhles Jr WC. GM-CSF with ganciclovir for the treatment of CMV retinitis in AIDS. Correspondence. New England Journal of Medicine 1560, 1989

Grundy JE, Shanley JD, Griffiths PD. Is cytomegalovirus interstitial pneumonitis in transplant recipients an immunopathological condition? Lancet 2: 996-999, 1987

Gudnason T, Belani KK, Balfour Jr HH. Ganciclovir treatment of cytomegalovirus disease in immunocompromised children. Pediatric Infectious Diseases Journal 8: 436-440, 1989

Harbison MA, De Girolami PC, Jenkins RL, Hammer SM. Ganciclovir therapy of severe cytomegalovirus infections in solid-organ transplant recipients. Transplantation 46: 82-88, 1988

Harris ML, Mathalone MBR. Intravitreal ganciclovir in CMV retinitis: case report. British Journal of Ophthalmology 73: 382-384, 1989

Hecht DW, Snydman DR, Crumpacker CS, Werner BG, Heinze-Lacey B, et al. Ganciclovir for treatment of renal transplant-associated primary cytomegalovirus pneumonia. Journal of Infectious Diseases 157: 187-190, 1988

Heery S, Hollows F. High-dose intravitreal gancyclovir for cytomegaloviral (CMV) retinitis. Australian and New Zealand Journal of Ophthalmology 17: 405-408, 1989

Heinemann M-H. *Staphylococcus epidermidis* endophthalmitis complicating intravitreal antiviral therapy of cytomegalovirus retinitis. Archives of Ophthalmology 107: 643-644, 1989

Henderly DE, Freeman WR, Causey DM, Rao NA. Cytomegalovirus retinitis and response to therapy with ganciclovir. Ophthalmology 94: 425-434, 1987

Henderson JR. Use of ganciclovir in the treatment of cytomegalovirus infections. British Journal of Clinical Pharmacology 43: 231-237, 1989

Henry K, Cantrill H, Fletcher C, Chinnock BJ, Balfour Jr HH. Use of intravitreal ganciclovir (dihydroxy propoxymethyl guanine) for cytomegalovirus retinitis in a patient with AIDS. American Journal of Ophthalmology 103: 17-23, 1987a

Henry K, Cantrill H, Kish MA. Intravitreous ganciclovir for patients receiving zidovudine. Correspondence. Journal of the American Medical Association 257: 3066, 1987b

Ho WG, Winston DJ, Champlin RE. Tolerance and efficacy of ganciclovir in the treatment of cytomegalovirus infections in immunosuppressed patients. Transplantation Proceedings 21: 3103-3106, 1989

Holland GN, Sidikaro Y, Kreiger AE, Hardy D, Sakamoto MJ. Treatment of cytomegalovirus retinopathy with ganciclovir. Ophthalmology 94: 815-823, 1987

Jabs DA, Newman C, De Bustros S, Polk BF. Treatment of cytomegalovirus retinitis with ganciclovir. Ophthalmology 94: 824-830, 1987

Jabs DA, Wingard JR, de Bustros S, de Miranda P, Saral R, et al. BW B759U for cytomegalovirus retinitis: intraocular drug penetration. Correspondence. Archives of Ophthalmology 104: 1436-1437, 1986

Jacobson MA, De Miranda P, Cederberg DM, Burnette T, Cobb E, et al. Human pharmacokinetics and tolerance of oral ganciclovir. Antimicrobial Agents and Chemotherapy 31: 1251-1254, 1987

Jacobson MA, De Miranda P, Gordon SM, Blum MR, Volberding P, et al. Prolonged pancytopenia due to combined ganciclovir and zidovudine therapy. Journal of Infectious Diseases 158: 489-490, 1988a

Jacobson MA, Mills J. Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS). Clinical findings, diagnosis, and treatment. Annals of Internal Medicine 108: 585-594, 1988

Jacobson MA, Mills J, Rush J, O'Donnell JJ, Miller RG, et al. Failure of antiviral therapy for acquired immunodeficiency syndrome-related cytomegalovirus myelitis. Archives of Neurology 45: 1090, 1988b

Jacobson MA, O'Donnell JJ, Brodie HR, Wofsy C, Mills J. Randomized prospective trial of ganciclovir maintenance therapy for cytomegalovirus retinitis. Journal of Medical Virology 25: 339-349, 1988c

Jacobson MA, O'Donnell JJ, Porteous D, Brodie HR, Feigal D, et al. Retinal and gastrointestinal disease due to cytomegalovirus in patients with the acquired immune deficiency syndrome: prevalence, natural history, and response to ganciclovir therapy. Quarterly Journal of Medicine 254: 473-486, 1988d

Jacobson MA, O'Donnell JJ, Rousell R, Dionian B, Mills J. Failure of adjunctive cytomegalovirus intravenous immune globulin to improve efficacy of ganciclovir in patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis: a phase 1 study. Antimicrobial Agents and Chemotherapy 34: 176-178, 1990

Kao GW, Peyman GA, Fiscella R, House B. Retinal toxicity of ganciclovir in vitrectomy infusion solution. Retina 7: 80-83, 1987

Katzenstein DA, Crane T, Jordan MC. Successful treatment of murine cytomegalovirus disease does not prevent latent virus infection. Journal of Laboratory and Clinical Medicine 108: 155-160, 1986

Keay S, Bissett J, Merigon TC. Ganciclovir treatment of cytomegalovirus infections in iatrogenically immunocompromised patients. Journal of Infectious Diseases 156: 1016-1021, 1987

Keay S, Petersen E, Icenogle T, Zeluff BJ, Samo T, et al. Ganciclovir treatment of serious cytomegalovirus infection in heart and heart-lung transplant recipients. Reviews of Infectious Disease 10 (Suppl. 3): S563-S572, 1988

Kern ER, Richards JT, Katz ME, Vogt PE, Overall JC. Treatment of experimental herpesvirus infections, with 9-(1,3-dihydroxy-2-propoxymethyl) guanine (DHPG). Abstract. Abstracts of the 1984 ICAAC, 1984

Klein RJ, Friedman-Kien AE. Effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine on the acute local phase of herpes simplex virus-induced skin infections in mice and the establishment of latency. Antimicrobial Agents and Chemotherapy 27: 763-768, 1985

Kotler DP, Culpepper-Morgan JA, Tierney AR, Klein EB. Treat-

ment of disseminated cytomegalovirus infection with 9-(1,3 dihydroxy-2-propoxymethyl)guanine: evidence of prolonged survival in patients with the acquired immunodeficiency syndrome. AIDS Research 2: 299-308, 1986

Lake KD, Fletcher CV, Love KR, Brown DC, Joyce LD, et al. Ganciclovir pharmacokinetics during renal impairment. Antimicrobial Agents and Chemotherapy 32: 1899-1900, 1988

Larder BA, Darby G. Susceptibility to other antiherpes drugs of pathogenic variants of herpes simplex virus selected for resistance to acyclovir. Antimicrobial Agents and Chemotherapy 29: 894-898, 1986

Laskin DL, Stahl-Bayliss CM, Kalman CM, Rosecan LR. Use of ganciclovir to treat serious cytomegalovirus infections in patients with AIDS. Journal of Infectious Diseases 155: 323-327, 1987b

Laskin OL, Cederberg DM, Mills J, Eron LJ, Mildvan D, et al. Ganciclovir for the treatment and suppression of serious infections caused by cytomegalovirus. American Journal of Medicine 83: 201-207, 1987a

Laskin OL, Kalman C, Stahl-Bayliss C. Pharmacokinetics, toxicity and clinical response of 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine in AIDS patients with cytomegalovirus infections. III World Conference on Clinical Pharmacology and Therapeutics, Stockholm Jul 27-Aug 1, 1986. Abstract. Acta Pharmacol Toxicol 59: 197, 1986

Lim W, Gupta A, Kahn E, Fagin J, Daum F, et al. Treatment of CMV enterocolitis with DHPG in an infant with AIDS. Abstract. Journal of Allergy and Clinical Immunology 81: 215, 1988

Lin J-C, Smith MC, Pagano JS. Prolonged inhibitory effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine against replication of Epstein-Barr virus. Journal of Virology 50: 50-55, 1984

Lin J-C, Smith MC, Pagano JS. Comparative efficacy and selectivity of some nucleoside analogs against Epstein-Barr virus. Antimicrobial Agents and Chemotherapy 27: 971-973, 1985

Littler A, Zeuthen J, McBride AA, Trøst Sørensen E, Powell KL, et al. Identification of an Epstein-Barr virus-coded thymidine kinase. EMBO Journal 5: 1959-1966, 1986

Macdonald EA. Treatment of cytomegalovirus retinitis in a patient with AIDS with 9-(1,3-dihydroxy-2-propoxymethyl)guanine. Canadian Journal of Ophthalmology 22: 48-52, 1987

Mar E-C, Cheng Y-C, Huang E-S. Effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine on human cytomegalovirus replication in vitro. Antimicrobial Agents and Chemotherapy 24: 518-521, 1983

Mar E-C, Chiou J-F, Cheng Y-C, Huang E-S. Inhibition of cellular DNA polymerase α and human cytomegalovirus-induced DNA polymerase by the triphosphates of 9-(2-hydroxyethoxymethyl)guanine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine. Journal of Virology 53: 776-780, 1985

Masdeu JC, Small CB, Weiss L, Elkin CM, Llena J, et al. Multifocal cytomegalovirus encephalitis in AIDS. Annals of Neurology 23: 97-99, 1988

Masur H, Lane HC, Palestine A, Smith PD, Manischewitz J, et al. Effect of 9-(1,3-dihydroxy-2-propoxymethyl) guanine on serious cytomegalovirus disease in eight immunosuppressed homosexual men. Annals of Internal Medicine 104: 41-44, 1986

Matthews T, Boehme R. Antiviral activity and mechanism of action of ganciclovir. Reviews of Infectious Diseases 10 (Suppl. 3): S490-S494, 1988

McLaren C, Chen MS, Ghazzouli I, Saral R, Burns WH. Drug resistance patterns of herpes simplex virus isolates from patients treated with acyclovir. Antimicrobial Agents and Chemotherapy 28: 740-744, 1985

Metselaar HJ, Weimar W. Cytomegalovirus infection and renal transplantation. Journal of Antimicrobial Chemotherapy 23 (Suppl. E): 37-47, 1989

Miller R, Storey J, Greco C, Gonzales M, Jacobsen M, et al. Subacute radiculomyelopathy caused by cytomegalovirus in patients with AIDS. Neurology 38 (Suppl. 1): 242, 1988

Milliken S, Powles R, Ettinger N, Gallagher C, Jameson B, et al. Ganciclovir in the treatment of cytomegalovirus pneumonitis in bone marrow transplant recipients. Transplantation Proceedings 21: 3110-3111, 1989

Moran DM, Kern ER, Overall Jr JC. Synergism between recombinant human interferon and nucleoside antiviral agents against herpes simplex virus: examination with an automated microtiter plate assay. Journal of Infectious Diseases 151: 1116-1122, 1985

Muntean W, Lackner H, Stünzner D, Ebner F. 9 Wochen alter Säugling mit konnataler Zytomegalieinfektion und Therapie mit Ganciclovir. Wiener Klinische Wochenschrift 101: 554-557, 1989

Naito T, Shiota H, Kanematsu S, Mimura Y, Ogawa T, et al. Studies on the cytotoxicity of a new anti-herpetic agent, 9-(1,3-dihydroxy-2-propoxymethyl) guanine, on the rabbit cornea (in Japanese). Nippon Ganka Gakkai Zasshi 92: 573-577, 1988

Nerenberg C, McClung S, Martin J, Fass M, La Fargue J, et al. A radioimmunoassay procedure for the determination of the antiviral nucleoside DHPG (9-[(1,3-dihydroxy-2-propoxy)-methyl]guanine) in plasma or serum. Pharmaceutical Research 3: 112-115, 1986

Nicholson ML, Flower AJE, Simpson A, Donnelly PK, Veitch PS, et al. Ganciclovir for severe cytomegalovirus infection in transplant recipients. Correspondence. Lancet 2: 1501-1502, 1988

O'Brien JJ, Campoli-Richards DM. Acyclovir - an updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 37: 233-309, 1989

O'Donnell JJ, Jacobson MA, Mills J. Development of cytomegalovirus (CMV) retinitis in a patient with AIDS during ganciclovir therapy for CMV colitis. Correspondence. New England Journal of Medicine 316: 1607-1608, 1987

Orellana J, Teich SA, Friedman AH, Lerebours F, Winterkorn J, et al. Combined short- and long-term therapy for the treatment of cytomegalovirus retinitis using ganciclovir (BW B759U). Ophthalmology 94: 831-838, 1987

Pagano JS, Sixbey JW, Lin J-C. Acyclovir and Epstein-Barr virus infection. Journal of Antimicrobial Chemotherapy 12 (Suppl. B): 113-121, 1983

Palestine AG, Stevens Jr G, Lane HC, Masur H, Fujikawa LS, et al. Treatment of cytomegalovirus retinitis with dihydroxy propoxymethyl guanine. American Journal of Ophthalmology 101: 95-101, 1986

Paya CV, Hermans PE, Smith TF, Rakela J, Wiesner RH, et al. Efficacy of ganciclovir in liver and kidney transplant recipients with severe cytomegalovirus infection. Transplantation 46: 229-234, 1988

Pepose JS, Newman C, Bach MC, Quinn TC, Ambinder RF, et al. Pathologic features of cytomegalovirus retinopathy after treatment with the antiviral agent ganciclovir. Ophthalmology 94: 414-424, 1987

Peyman GA, Schulman JA, Khoobehi B, Alkan HM, Tawakol ME, et al. Toxicity and clearance of a combination of liposome-encapsulated ganciclovir and trifluridine. Retina 9: 232-236, 1989

Pinching AJ. Cytomegalovirus infection in the acquired immune deficiency syndrome. Journal of Antimicrobial Chemotherapy 23 (Suppl. E): 31-36, 1989

Plotkin SA, Drew WL, Felsenstein D, Hirsch MS. Sensitivity of clinical isolates of human cytomegalovirus to 9-(1,3-dihydroxy-2-propoxymethyl)guanine. Journal of Infectious Diseases 152: 833-834, 1985

Pulido J, Peyman GA, Lesar T, Vernot J. Intravitreal toxicity of hydroxyacyclovir (BW-B759U), a new antiviral agent. Archives of Ophthalmology 103: 840-841, 1985

Pulliam L, Panitch HS, Baringer JR, Dix RD. Effect of antiviral

agents on replication of herpes simplex virus type 1 in brain cultures. Antimicrobial Agents and Chemotherapy 30: 840-846, 1986

Rasmussen L, Chen PT, Mullenax JG, Merigan TC. Inhibition of human cytomegalovirus replication by 9-(1,3-dihydroxy-2-propoxymethyl)guanine alone and in combination with human interferons. Antimicrobial Agents and Chemotherapy 26: 441-445, 1984

Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Annals of Internal Medicine 109: 783-788, 1988a

Reed EC, Shepp DH, Dandliker PS, Meyers JD. Ganciclovir treatment of cytomegalovirus infection of the gastrointestinal tract after marrow transplantation. Bone Marrow Transplantation 3: 199-206, 1988b

Richards DM, Carmine AA, Brogden RN, Heel RC, Speight TM, et al. Acyclovir: a review of its pharmacodynamic properties and therapeutic efficacy. Drugs 26: 378-438, 1983

Robinson MR, Teitelbaum C, Taylor-Findlay C. Thrombocytopenia and vitreous haemorrhage complicating ganciclovir treatment. American Journal of Ophthalmology 107: 560-561, 1989

Rook AH. Interactions of cytomegalovirus with the human immune system. Reviews of Infectious Diseases 10 (Suppl. 3): S460-S467, 1988

Rosecan LR, Laskin OL, Kalman CM, Haik BG, Ellsworth RM. Antiviral therapy with ganciclovir for cytomegalovirus retinitis and bilateral exudative retinal detachments in an immunocompromised child. Ophthalmology 93: 1401-1407, 1986

Rostoker G, Ben Maadi A, Buisson C, Deforge L, Weil B, et al. Ganciclovir for severe cytomegalovirus infection in transplant recipients. Correspondence. Lancet 2: 1137-1138, 1988

Rubin RH, Lynch P, Pasternack MS, Schoenfeld D, Medearis Jr DN. Combined antibody and ganciclovir treatment of murine cytomegalovirus-infected normal and immunosuppressed BALB/c mice. Antimicrobial Agents and Chemotherapy 33: 1975-1979, 1989

Rush J, Mills J. Effect of combinations of difluoromethylornithine (DFMO) and 9[1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG) on human cytomegalovirus. Journal of Medical Virology 21: 269-276, 1987

Russler SK, Tapper MA, Carrigan DR. Susceptibility of human herpesvirus 6 to acyclovir and ganciclovir. Correspondence. Lancet 2: 382, 1989

Schmidt GM, Kovacs A, Zaia JA, Horak DA, Blume KG, et al. Ganciclovir/immunoglobulin combination therapy for the treatment of human cytomegalovirus-associated interstitial pneumonia in bone marrow allograft recipients. Transplantation 46: 905-907, 1988

Schulman J, Fiscella R, Peyman GA, Pulido J, Horton MB, et al. Intraocular 9-([2-hydroxy-1-(hydroxymethyl)ethoxy]methyl) guanine levels after intravitreal and subconjunctival administration. Ophthalmic Surgery 17: 429-432, 1986a

Schulman J, Peyman GA, Horton MB, Liu J, Barber JC, et al. Intraocular penetration of new antiviral agent, hydroxyacyclovir (BW-B759U). Japanese Journal of Ophthalmology 30: 116-124, 1986b

Selby P, Powles RL, Jameson B, Stolle K, Tryhorn Y, et al. Treatment of cytomegalovirus pneumonitis after bone marrow transplantation with 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine Correspondence. Lancet 2: 1377-1378, 1986

Shanley JD, Morningstar J, Jordan MC. Inhibition of murine cytomegalovirus lung infection and interstitial pneumonitis by acyclovir and 9-(1,3-dihydroxy-2-propoxymethyl)guanine. Antimicrobial Agents and Chemotherapy 28: 172-175, 1985

Shanley JD, Pomeroy C, Via CS, Shearer GM. Interstitial pneumonitis during murine cytomegalovirus infection and graft-versus-host reaction: effect of ganciclovir therapy. Journal of Infectious Diseases 158: 1391-1394, 1988

Shepp DH, Dandliker PS, de Miranda P, Burnette TC, Cederberg DM, et al. Activity of 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine in the treatment of cytomegalovirus pneumonia. Annals of Internal Medicine 103: 368-373, 1985

Shiota H, Naito T, Mimura Y. Anti-herpes simplex virus (HSV) effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG) in rabbit cornea. Current Eye Research 6: 241-245, 1987

Sinnott JT, Cullison JP, Rogers K. Treatment of cytomegalovirus gastrointestinal ulceration in a heart transplant patient. Journal of Heart Transplantation 6: 186-188, 1987

Smee DF. Interaction of 9-(1,3-dihydroxy-2-propoxymethyl)guanine with cytosol and mitochondrial deoxyguanosine kinases: possible role in anti-cytomegalovirus activity. Molecular and Cellular Biochemistry 69: 75-81, 1985

Smee DF, Boehme R, Chernow M, Binko BP, Matthews TR. Intracellular metabolism and enzymatic phosphorylation of 9-(1,3-dihyhdroxy-2-propoxymethyl)guanine and acyclovir in herpes simplex virus-infected and uninfected cells. Biochemical Pharmacology 34: 1049-1056, 1985a

Smee DF, Campbell NL, Matthews TR. Comparative anti-herpesvirus activities of 9-(1,3-dihydroxy-2-propoxymethyl)guanine, acyclovir, and two 2′-fluoropyrimidine nucleosides. Antiviral Research 5: 259-267, 1985b

Smee DF, Knight SS, Duke AE, Robinson WS, Matthews TR, et al. Activities of arabinosyladenine monophosphate and 9-(1,3-dihydroxy-2-propoxymethyl)guanine against ground squirrel hepatitis virus in vivo as determined by reduction in serum virion-associated DNA polymerase. Antimicrobial Agents and Chemotherapy 27: 277-279, 1985c

Smee DF, Martin JC, Verheyden JPH, Matthews TR. Anti-herpesvirus activity of the acyclic nucleoside 9-(1,3-dihydroxy-2-propoxymethyl)guanine. Antimicrobial Agents and Chemotherapy 23: 676-682, 1983

Smith KO, Galloway KS, Kennell WL, Ogilvie KK, Radatus BK. A new nucleoside analog, 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine, highly active in vitro against herpes simplex virus types 1 and 2. Antimicrobial Agents and Chemotherapy 22: 55-61, 1982a

Smith KO, Galloway KS, Ogilvie KK, Cheriyan UO. Synergism among BIOLF-62, phosphonoformate, and other antiherpetic compounds. Antimicrobial Agents and Chemotherapy 22: 1026-1030, 1982b

Smith KO, Hodges SL, Kennell WL, Galloway KS, Poirier RH, et al. Experimental ocular herpetic infections in rabbits. Treatment with 9-([2-hydroxy-1-(hydroxymethyl)ethoxy]methyl)-guanine. Archives of Ophthalmology 102: 778-781, 1984

Smith PD, Lane HC, Gill VJ, Manischewitz JF, Quinnan GV, et al. Intestinal infections in patients with the acquired immunodeficiency syndrome (AIDS) - etiology and response to therapy. Annals of Internal Medicine 108: 328-333, 1988

Snydman DR. Ganciclovir therapy for cytomegalovirus disease associated with renal transplants. Reviews of Infectious Diseases 10 (Suppl. 3): S554-S562, 1988

Sommadossi J-P, Bevan R. High-performance liquid chromatographic method for the determination of 9-(1,3-dihydroxy-2-propoxymethyl)guanine in human plasma. Journal of Chromatography 414: 429-433, 1987

Sommadossi J-P, Bevan R, Ling T, Lee F, Mastre B, et al. Clinical pharmacokinetics of ganciclovir in patients with normal and impaired renal function. Reviews of Infectious Diseases 10 (Suppl. 3): S507-S514, 1988

Sommadossi J-P, Carlisle R. Toxicity of 3′-azido-3′-deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine for normal human hematopoietic progenitor cells in vitro. Antimicrobial Agents and Chemotherapy 31: 452-454, 1987

Stoffel M, Pirson Y, Squifflet JP, Lamy M, Gianello P, et al.

Treatment of cytomegalovirus pneumonitis with ganciclovir in renal transplantation. Transplantation International 1: 181-185, 1988

St Clair MH, Lambe CU, Furman PA. Inhibition by ganciclovir of cell growth and DNA synthesis of cells biochemically transformed with herpesvirus genetic information. Antimicrobial Agents and Chemotherapy 31: 844-849, 1987

St Clair MH, Miller WH, Miller RL, Lambe CU, Furman PA. Inhibition of cellular α DNA polymerase and herpes simplex virus-induced DNA polymerases by the triphosphate of BW759U. Antimicrobial Agents and Chemotherapy 25: 191-194, 1984

Stein DS, Verano AS, Levandowski RA. Successful treatment with ganciclovir of disseminated cytomegalovirus infection after liver transplantation. American Journal of Gastroenterology 83: 684-686, 1988

Tadepalli SM, Quinn RP, Averett DR. A competitive enzyme-linked immunosorbent assay to quantitate acyclovir and BW B759U in human plasma and urine. Antimicrobial Agents and Chemotherapy 29: 93-98, 1986

Taylor DL, Jeffries DJ, Taylor-Robinson D, Parkin JM, Tyms AS. The susceptibility of adenovirus infection to the anti-cytomegalovirus drug, ganciclovir (DHPG). FEMS Microbiology Letters 49: 337-341, 1988

Teich SA, Castle J, Friedman AH, Siroty W, Orellana J, et al. Active cytomegalovirus particles in the eyes of an AIDS patient being treated with 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (ganciclovir). British Journal of Ophthalmology 72: 293-298, 1988

Thomson MH, Jeffries DJ. Ganciclovir therapy in iatrogenically immunosuppressed patients with cytomegalovirus disease. Journal of Antimicrobial Chemotherapy 23 (Suppl. E): 61-70, 1989

Tocci MJ, Livelli TJ, Perry HC, Crumpacker CS, Field AK. Effects of the nucleoside analog 2'-nor-2'-deoxyguanosine on human cytomegalovirus replication. Antimicrobial Agents and Chemotherapy 25: 247-252, 1984

Tolman RL, Field AK, Karkas JD, Wagner AF, Germershausen J, et al. 2'-nor-cGMP: a *seco*-cyclic nucleotide with powerful anti-DNA-viral activity. Biochemical and Biophysical Research Communications 128: 1329-1335, 1985

Topiel MS, Kutscher JJ, Pilipshen SJ, Quinton KJ. Cytomegalovirus infection, 9-(1,3-dihydroxy-2-propoxymethyl)guanine, and Crohn's Disease. Correspondence. Annals of Internal Medicine 105: 302, 1986

Trousdale MD, Nesburn AB, Willey DE, Taaid H. Efficacy of BW759 (9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine) against herpes simplex virus type 1 keratitis in rabbits. Current Eye Research 3: 1007-1015, 1984

Tucker P, Nordin MC, Silver M, Sobotka P, Robinson J, et al. A favorable experience with ganciclovir in the treatment of cytomegalovirus pneumonia in heart transplant patients. Abstract. Clinical Research 35: 860A, 1987

Turner PA, Rytel MW, Taft TA. Use of 9-(2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine in serious cytomegalovirus infections in the immunocompromised. Clinical Research 34: 924A, 1986

Tyms AS, Davis JM, Clarke JR, Jeffries DJ. Synthesis of cytomegalovirus DNA is an antiviral target late in virus growth. Journal of General Virology 68: 1563-1573, 1987

Tyms AS, Davis JM, Jeffnes DJ, Meyers JD. BWB759U, an analogue of acyclovir, inhibits human cytomegalovirus in vitro. Correspondence. Lancet 2: 924-925, 1984

Ussery FM, Gibson SR, Conklin RH, Piot DF, Stool EW, et al. Intravitreal ganciclovir in the treatment of AIDS-associated cytomegalovirus retinitis. Ophthalmology 95: 640-648, 1988

van der Horst CM, Lin J-C, Raab-Traub N, Smith MC, Pagano JS. Differential effects of acyclovir and 9-(1,3-dihydroxy-2-propoxymethyl)guanine on herpes simplex virus and Epstein-Barr virus in a dually infected human lymphoblastoid cell line. Journal of Virology 61: 607-610, 1987

Verdonck LF, de Gast GC, Dekker AW, de Weger RA, Schuurman H-J, et al. Treatment of cytomegalovirus pneumonia after bone marrow transplantation with cytomegalovirus immunoglobulin combined with ganciclovir. Bone Marrow Transplantation 4: 187-189, 1989

Visser OHE, Bos PJM. Kaposi's sarcoma of the conjunctiva and CMV-retinitis in AIDS. Documenta Ophthalmologica 64: 77-85, 1986

Watson FS, O'Connell JB, Amber IJ, Renlund DG, Classen D, et al. Treatment of cytomegalovirus pneumonia in heart transplant recipients with 9(1,3-dihydroxy-2-propoxymethyl)-guanine (DHPG). Journal of Heart Transplantation 7: 102-105, 1988

Weller S, Liao SHT, Cederberg DM, de Miranda P, Blum MR. The pharmacokinetics of ganciclovir in patients with cytomegalovirus (CMV) infections. Journal of Pharmaceutical Sciences 76: S120, 1987

Wilson EJ, Medearis Jr DN, Hansen LA, Rubin RH. 9-(1,3-dihydroxy-2-propoxymethyl)guanine prevents death but not immunity in murine cytomegalovirus-infected normal and immunosuppressed BALB/c mice. Antimicrobial Agents and Chemotherapy 31: 1017-1020, 1987

Winston DJ, Ho WG, Bartoni K, Holland GN, Mitsuyasu RT, et al. Ganciclovir therapy for cytomegalovirus infections in recipients of bone marrow transplants and other immunosuppressed patients. Reviews of Infectious Diseases 10 (Suppl. 3): S547-S553, 1988

Woolf NK, Ochi JW, Silva EJ, Sharp PA, Harris JP, et al. Ganciclovir prophylaxis for cochlear pathophysiology during experimental guinea pig cytomegalovirus labyrinthitis. Antimicrobial Agents and Chemotherapy 32: 865-872, 1988

Wreghitt T. Cytomegalovirus infections in heart and heart-lung transplant recipients. Journal of Antimicrobial Chemotherapy 23 (Suppl. E): 49-60, 1989

Authors' address: *Diana Faulds*, ADIS Press Limited, 41 Centorian Drive, Private Bag, Mairangi Bay, Auckland 10, New Zealand.