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Comparative Tolerability of Therapies for Cytomegalovirus Retinitis

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Abstract

Cytomegalovirus (CMV) retinitis is a potentially sight-threatening complication of advanced HIV infection. The acute infection can be controlled with one of several therapies, including intravenous ganciclovir, foscarnet or cidofovir, slow release ganciclovir intraocular implants or serial intraocular injections of ganciclovir or foscarnet. The initial induction course of therapy is typically followed by lifelong maintenance therapy. In addition to the aforementioned treatments, oral ganciclovir and intravitreal fomivirsen injections are other options for maintenance therapy.

The choice of agent must take into consideration factors such as comparative short and long term toxicity of the agents, route of administration and the possible need for indwelling catheters, administration time, cost and protection afforded against systemic dissemination of CMV infection. Possible drug interactions and additive toxicities of other agents needed for the management of the underlying HIV infection must also be taken into consideration. These factors can affect the tolerability of therapy as well as the quality of life of the patient.

Relapse or progression of CMV retinitis may be caused by either inadequate drug concentrations at the site of the infection or by drug resistance. This may necessitate either an increase in drug dosage, a change in route of administration or a change to an alternative agent. All of these approaches can increase the risk of toxicity of the therapy.

With the initiation of highly active antiretroviral therapy and partial reconstitution of the immune system, some patients have been able to successfully discontinue anti-CMV maintenance therapy, thereby decreasing long term drug toxicity. Determination of the patient predictors of success of this approach is an active area of research.

Cytomegalovirus (CMV) retinitis is a potentially sight-threatening complication of advanced HIV infection. Patients may complain of visual flashers, floaters, blurred vision or blind spots, or the infection may be asymptomatic and is diagnosed by the characteristic appearance of exudate and haemorrhage on fundoscopic examination.

Prior to the widespread use of combination antiretroviral therapy, cytomegalovirus disease, usually retinitis, complicated HIV infection in approximately 30 to 40% of patients with CD4+ lymphocyte counts <50/mm^3.[1,2] With the use of highly active antiretroviral therapy, the incidence of this complication has decreased dramatically.[3-5]

Many agents are available to treat cytomegalovirus infection including intravenous formulations (ganciclovir, foscarnet and cidofovir), slow release ganciclovir intraocular implants, and intraocular injections of ganciclovir or foscarnet. A higher dose induction course (2 to 3 weeks) is followed by lower dose long term maintenance therapy in attempts to delay the inevitable progression of the retinitis. Treatment was usually required for life, but with the current changes in the clinical course of cytomegalovirus retinitis, this is being re-evaluated.[6-9] Although few directly comparative trials are available, the efficacy of the different treatments is similar, and in most clinical situations more than one treatment option is appropriate.

Choices are often based on the differential toxicity of the agents, the need for long term intravenous catheters, infusion times, cost, reimbursement, and other quality of life issues. Consideration must be given to the unique characteristics of the ocular disease, patient preference, the presence or risk of extraocular cytomegalovirus infection, concomitant therapy, underlying medical conditions and the patient's lifestyle and living conditions.

In this review, we compare and contrast the major adverse effects associated with the various treatment modalities for CMV retinitis in HIV with incidence rates from controlled clinical trials where available (table I). We include recommendations on monitoring and management of certain toxicities, including dosage adjustments for renal insufficiency (table II). Most of the data are derived from studies conducted prior to the use of highly active antiretroviral therapy.

1. Intravenous Ganciclovir

Ganciclovir was the first drug to show efficacy in HIV-associated CMV retinitis, with 80 to 100% of patients demonstrating a partial or complete response.[10,17-24] Without the use of continuous

maintenance therapy (5 mg/kg/day), relapse was inevitable, typically 20 to 40 days after the completion of induction therapy.[10,17,20,22-25] Even with continuous maintenance therapy, relapses occurred with a median time to progression of 42 to 109 days.[15,19,23,26-31] Higher doses (5 mg/kg twice daily) may be more effective than standard doses but have not been compared in randomised trials, and may be associated with increased toxicity.[32-34] Use of a lowered maintenance dosage (3 mg/kg/day) is associated with more rapid rates of progression, within a median time of 31 to 47 days.[10] Long term maintenance therapy requires the insertion of an indwelling central venous catheter.

1.1 Common Adverse Reactions

1.1.1 Haematological Events

Granulocytopenia, anaemia and thrombocytopenia are the most common dose-limiting adverse effects. The exact incidence is difficult to compare between studies because of differences in definitions, duration of therapy, concomitant medications and protocol-mandated dose modifications.

Granulocytopenia

Granulocytopenia (<500/mm^3) has been reported in 16 to 34% of patients within the first 6 months of therapy.[18-30,35] This adverse effect is dose related and reversible, with recovery 5 to 7 days after drug discontinuation. Because of the theoretical increased risk of bacterial infections, dose interruption is recommended if the neutrophil count drops below 500/mm^3. However, the actual risk of severe infection is unknown, and lower levels of neutropenia may be tolerated. Haematological growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are frequently used to enable continued administration of full dose ganciclovir. These growth factors are usually given at doses of 5 μg/kg subcutaneously with tapering to maintain the neutrophil count at >500 to 1000/mm^3. The use of G-CSF and GM-CSF can also be associated with additional toxicity, including injection site reactions, fever, myalgia, arthralgias, malaise, hypotension, fluid retention, headaches and bone pain. Eosinophilia is a frequent complication of GM-CSF. The use of growth factors also adds a significant additional cost. An increase in HIV p24 antigen levels has been reported in some patients with AIDS receiving GM-CSF,[36,37] raising the concern of induction of HIV proliferation, but increases in plasma viraemia were not seen in a small study of patients on combination antiretroviral therapy, including a protease inhibitor.[38]

In study ACTG-073, concurrent use of GM-CSF and IV ganciclovir was found to decrease the risk of neutropenia from 45 to 12.5% and was associated with fewer missed doses of ganciclovir and a trend towards a delay in time to first progression of CMV retinitis.[39] Similarly, concurrent use of G-CSF has been shown to delay the onset of ganciclovir-induced neutropenia.[40]

Thrombocytopenia

Thrombocytopenia <20 000 $\times$ 10^9/mm^3 and <50 000 $\times$ 10^9/mm^3 has been reported in 3 to 5% and 9 to 19% of patients, respectively.[18,22-24,30,35] Because of the risk of bleeding, dose interruption is recommended if platelet counts fall below 25 000 $\times$ 10^9 cells/mm^3.

Anaemia

Dose dependent anaemia (haemoglobin <8 g/dl) has been reported in 24 to 43% of patients within 6 months of the initiation of ganciclovir.[23,30,35] The anaemia typically responds to transfusion, but if it is recurrent, dosage modification or switch to an alternative agent may be required.

Patients receiving ganciclovir should have regular monitoring of their complete blood count and differential at least weekly during induction and maintenance and up to twice weekly if toxicity develops. Alternative forms of treatment should be considered if the patient has haematological abnormalities before treatment, such as haemoglobin <8 g/dl, neutrophil count <500/mm^3 or platelet count <25 000 $\times$ 10^9/mm^3.

1.1.2 Other Adverse Events

Central nervous system adverse events, including confusion, hallucinations, seizures, psychosis,

Table I. Comparison of agents for antiviral therapy for cytomegalovirus (CMV) infection[10-16]

	Cidofovir	Ganciclovir	Foscarnet
Structure	1-[(S)-3-hydroxy-2-(phosphonomethoxy)propyl]cytosine dihydrate	9-(1,3-dihydroxyl-2-propoxymethyl) guanine	Trisodium phosphonoformate
Pharmacology	Nucleotide analogue; phosphorylated by cellular enzymes to active metabolite, cidofovir diphosphate	2-deoxyguanosine analogue; phosphorylated by virally encoded enzymes to ganciclovir-triphosphate	Pyrophosphate analogue; does not require activation (phosphorylation)
Mechanism of action	Selectively inhibits CMV DNA polymerase	Inhibition of viral DNA synthesis by 2 modes: competitive inhibition of viral DNA polymerase, and incorporation into DNA causing chain termination	Selectively inhibits viral DNA polymerase at the pyrophosphate binding site
In vitro activity	Active against CMV and other herpesviruses: wild type CMV (0.5-2.8); HSV-1, HSV-2 (12.7-31.7); VZV (0.79); EBV (0.03); HHV-6 (<6.3)[a]	Active against CMV and other herpesviruses: HSV (2.4); CMV (0.4-11); VZV (32); EBV (1)[a]	Active against CMV and other herpesviruses: CMV (50-800); HSV-1, HSV-2 (10-130); VZV (48-90); EBV (<500); HHV-6 (<67); ganciclovir-resistant CMV (190)[a]
Pharmacokinetics	**Intravenous (5 mg/kg + oral probenecid):** AUC 40.8 mg • h/L; C_{max} 19.6 mg/L; Vd_{ss} 0.41 L/kg; <6% bound to plasma proteins; intracellular $t_{½}$ 17-30h	**Intravenous (5 mg/kg):** AUC 22-26.8 mg • h/L; C_{max} 8-9 mg/L; $t_{½}$ 2.9h. **Oral:** bioavailability 6-9% with food; AUC 15 mg • h/L; C_{max} 1.1 mg/L. **Intravitreal (200μg injection):** C_{max} 63.86 μmol/L; $t_{½}$ 13.3h; Vd 11.7ml. **Intraocular implant: (1μg/h):** C_{ss} 16.06 μmol/L	**Intravenous (60 mg/kg q8h):** C_{max} 509 μmol/L; C_{min} 98 μmol/L; Vd_{ss} 0.52-0.74 L/kg; 82-86% renally cleared; $t_{½}$ 3.3-6.8h. **Intravitreal (1200**μg injection): $t_{½}$ 32h; Vd 5.9ml; concentrations of 292-409 μmol/L (23.25-49.5h post injection)
Dosage regimen: systemic	**Induction:** 5 mg/kg IV (over 1h) once weekly for 2wk[b] **Maintenance:** 5 mg/kg IV (over 1h) once every 2wk[b]	**Induction:** 5 mg/kg IV (over 1h) q12h for 14-21 days **Maintenance:** 5 mg/kg IV (over 1h) daily, or 6 mg/kg/day IV for 5 days per week; or, 1000mg po tid with food	**Induction:** 60 mg/kg IV (over ≥1h) q8h, or 90 mg/kg IV q12h **Maintenance:** 90-120 mg/kg/day (over 2h)
Dosage regimen: intraocular	Not recommended	**Intravitreal injection:** *Induction:* 200-400μg injections every 2-3 days *Maintenance:* 200-400μg injection weekly **Intraocular implant:** 4.5mg implant releasing 1 μg/h; replace every 6-8mo	**Intravitreal injection:** *Induction:* 1200-2400μg injections every 2-3 days *Maintenance:* 1200-2400μg injection weekly
Adverse effects: systemic	Dose-dependent nephrotoxicity (including proteinuria, azotaemia, ↑ serum creatinine level, and rarely metabolic acidosis), neutropenia, ocular hypotony, fever, infection, dyspnoea, nausea/vomiting, diarrhoea, and asthenia	Neutropenia, thrombocytopenia, headache, confusion, diarrhoea, nausea, abnormal liver function values, fever, rash	Nephrotoxicity, mineral and electrolyte imbalances, headache, seizures, anaemia, fever, nausea/vomiting, diarrhoea, fatigue
Adverse effects: local administration	Hypotony, iritis, retinal detachment	**Transient events:** ↑ intraocular pressure, pain, total amaurosis. **Other events:** endophthalmitis, retinal detachment, vitreal haemorrhage, optic atrophy	**Transient events:** ↑ intraocular pressure, pain, total amaurosis **Other events:** endophthalmitis, retinal detachment, vitreal haemorrhage, optic atrophy
Other considerations	Administer at least 1L saline with each dose. Adjust dosage in renal dysfunction	Contraindicated in pregnant women; monitor for haematological toxicities, adjust dosage in renal dysfunction	Administer via infusion pump; ensure adequate hydration. Adjust dosage in renal dysfunction

Continued on next page

Table I. Contd

	Cidofovir	Ganciclovir	Foscarnet
Drug interactions	**Nephrotoxins** (e.g., aminoglycosides, amphotericin B, foscarnet, pentamidine IV: risk of additive nephrotoxicity – avoid concomitant administration if possible). **Renally excreted agents:** Probenecid may interact with metabolism or renal tubular excretion of many drugs. Monitor for toxicity and adjust dosage if necessary on day of probenecid administration	**Zidovudine:** ↑ risk of neutropenia, anaemia. Hold or decrease zidovudine dose during ganciclovir induction therapy. Consider using colony-stimulating factor if necessary. **Didanosine:** 70-100% ↑ didanosine concentration and 20% ↓ ganciclovir concentration. Monitor for didanosine toxicity (e.g., diarrhoea, pancreatitis, peripheral neuropathy) and progression of CMV disease **Imipenem:** ↑ risk of seizures. Do not exceed 2g/day of imipenem. Adjust dosage of both agents in renal failure **Probenecid:** 50% ↑ ganciclovir AUC. Avoid concomitant use due to potential for: ↑ risk of dose-related ganciclovir toxicities, risk of probenecid adverse effects (e.g., headache, gastrointestinal upset, rash, etc.), and interference with renal elimination of other drugs **Other myelosuppressive agents** (e.g., amphotericin B, dapsone, flucytosine, pentamidine IV, primaquine, pyrimethamine, TMP-SMX, trimetrexate): risk of bone marrow toxicity. Use together with caution	**Nephrotoxins** (e.g., aminoglycosides, amphotericin B, foscarnet, pentamidine IV: risk of additive nephrotoxicity – avoid concomitant administration if possible). Adjust dosages of both drugs in renal failure
Supplied as:	375 mg/5ml nonpreserved single-use vial	500mg sterile powder, 250mg capsules, 1 μg/h ocular implant	24 mg/ml solution for injection (250ml and 500ml bottles)

a Concentration inhibiting 50% of strains (μmol/L) is shown in brackets after each virus.

b Administered with probenecid.

AUC = area under the concentration-time curve; $\mathbf{C_{max}}$ = maximum (peak) plasma drug concentration after single-dose administration; $\mathbf{C_{min}}$ = minimum plasma concentration; **EBV** = Epstein-Barr virus; **HHV** = human herpes virus; **HSV** = Herpes simplex virus; **IV** = intravenous; **po** = orally; **q8, 12h** = every 8, 12 hours; $\mathbf{t_{½}}$ = plasma elimination half-life; **tid** = 3 times daily; **TMP-SMX** = trimethoprim-sulfamethoxazole (cotrimoxazole); $\mathbf{V_d}$ = apparent volume of distribution; $\mathbf{Vd_{ss}}$ = Vd at steady state; **VZV** = Varicella zoster virus; ↑ = increased; ↓ = decreased.

abnormal thought patterns, change in mental status, nightmares, anxiety, tremors, ataxia and headaches have been reported in 3 to 5% of patients.[35]

Gastrointestinal adverse effects such as anorexia, nausea, vomiting and diarrhoea are reported in up to 6% of patients. Elevations in liver transaminase levels have been reported in 2% of recipients.

Other reported symptoms include fever (2 to 5%), oedema (<1%), and myalgias (2 to 6%). Increases in serum creatinine levels >221 μmol/L have been reported in up to 6% of patients.[35] Consequently, serum creatinine level should be measured weekly during induction therapy and at least every 2 to 4 weeks on maintenance therapy. Dose adjustments should be made if renal insufficiency occurs (table II).

Azoospermia has been observed in animals as a result of direct inhibition of sperm-producing cells. There was no observed effect on testicular or endocrine function. Decreased fertility may also occur in female animals. Ganciclovir has been associated with birth defects in animals and should not be used during pregnancy. It causes tumours in animals, and although no human data are available, it should be considered a potential carcinogen.[10]

2. Oral Ganciclovir

An oral formulation of ganciclovir has been licensed for maintenance therapy in CMV retinitis.

Table II. Dosage guidelines for adjustment of systemic agents for cytomegalovirus retinitis for patients with renal impairment[10,11,15]

Creatinine clearance (L/h) [ml/min][a]	Intravenous dose		Other
	induction	maintenance	
Cidofovir			
2.46-3.3 [41-55]	2 mg/kg weekly × 2wk	2 mg/kg every 2wk	Intravenous normal saline and oral probenecid must accompany each cidofovir infusion
1.8-2.4 [30-40]	1.5 mg/kg weekly × 2wk	1.5 mg/kg every 2wk	
1.2-1.74 [20-29]	1 mg/kg weekly × 2wk	1 mg/kg every 2wk	
≤1.14 [≤19]	0.5 mg/kg weekly × 2wk	0.5 mg/kg every 2wk	
Foscarnet			
>0.084 [>1.4]/kg	90 mg/kg q12h	90-120 mg/kg q24h	Determine CrCl at baseline, 2-3 times per week during induction, and every 1-2wk during maintenance. Adjust foscarnet dose as required. Ensure adequate hydration
0.084-0.06 [1.4-1.0]/kg	70 mg/kg q12h	70-90 mg/kg q24h	
0.06-0.048 [1.0-0.8]/kg	50 mg/kg q12h	50-65 mg/kg q24h	
0.048-0.036 [0.8-0.6]/kg	80 mg/kg q24h	80-105 mg/kg q48h	
0.036-0.03 [0.6-0.5]/kg	60 mg/kg q24h	60-80 mg/kg q48h	
0.03-0.024 [0.5-0.4]/kg	50 mg/kg q24h	50-65 mg/kg q48h	
<0.024 [<0.4]/kg	Not recommended	Not recommended	
Ganciclovir			Oral maintenance dosage
4.2 [70]	5 mg/kg q12h	5 mg/kg q24h	1000mg tid or 500mg q3h (6 × day)
3.0-4.14 [50-69]	2.5 mg/kg q12h	2.5 mg/kg q24h	1500mg daily or 500mg tid
1.5-2.94 [25-49]	2.5 mg/kg q24h	1.25 mg/kg q24h	1000mg daily or 500mg bid
0.6-1.44 [10-24]	1.25 mg/kg q24h	0.625 mg/kg q24h	500mg daily
<0.6 [<10]	1.25 mg/kg 3 times weekly, following haemodialysis	0.625 mg/kg q24h 3 times weekly, following haemodialysis	500mg 3 times weekly, following haemodialysis

a Creatinine clearance can be calculated from the following formula: $\text{CrCl (ml/min)} = \frac{(140 - \text{age, years}) \text{ (ideal bodyweight, kg)} \times 60}{50 \times (\text{serum creatinine, } \mu\text{mol/L})}$

For female patients, value is 0.85 × above value.

bid = twice daily; **CrCl** = creatinine clearance; **q3, 12, 24, 48h** = every 3, 12, 24, 48h; **tid** = 3 times daily.

The drug is administered as 1g (4 × 250mg capsules) every 8 hours. At this dosage, serum concentrations are approximately 70% of those observed with intravenous ganciclovir. The oral bioavailability of ganciclovir is low, (6 to 9%), but increases when taken with food.[41] Oral ganciclovir should not be used for induction therapy. It has been compared with intravenous ganciclovir for maintenance therapy of CMV retinitis in 3 randomised open labelled multicentre studies.[31,42,43] The mean time to progression using masked retinal photographs was 62 to 66 days in the intravenous group versus 51 to 57 days in the oral group. Higher doses of oral ganciclovir (4.5 to 6 g/day) have greater efficacy.[44]

Although the oral formulation is a well tolerated alternative in maintenance therapy, careful monitoring is crucial to check for disease progression. Because of the consistent trend towards poorer control of retinitis compared with intravenous therapy, oral ganciclovir should not be used, or used only with caution, in patients at high risk of losing their vision.[45] This would include: (i) patients whose retinitis is not stable after 3 to 4 weeks of intravenous induction therapy; (ii) patients who have zone 1 disease, i.e. CMV retinitis involving the macular or optic disc where progression could lead to a rapid loss of vision; (iii) blindness in the other eye. Oral ganciclovir should also not be used in patients with moderate to severe diarrhoea which could impair drug absorption.

Since the use of highly active antiretroviral therapy for HIV, the rate and incidence of relapsed retinitis has decreased. Consequently oral ganciclovir has increasingly become the agent of choice for maintenance therapy.[46,47]

The oral form is cost-saving for maintenance therapy, with the major cost savings attributable to

the decrease in home care expenditures.[48] An obvious advantage is lack of need for the indwelling intravenous catheter.

2.1 Common Adverse Reactions

The incidence and type of adverse reactions are similar between the oral and intravenous forms of ganciclovir. Anaemia was reported less commonly with oral ganciclovir in one study, (15 versus 24%; p = 0.02) but the incidences of neutropenia, thrombocytopenia and gastrointestinal adverse effects were not statistically different.[31] In another study, the incidence of anaemia was not found to be different between the 2 groups.[42] The incidence of sepsis was not statistically different between the groups receiving oral or intravenous therapy.[31,42]

3. Intravenous Foscarnet

Clinical studies have shown a clinical response rate of 80 to 90% for intravenous foscarnet in HIV-associated CMV retinitis.[49-53] For administration by means of a peripheral vein, foscarnet solution (24 g/L) must be diluted to 12 g/L with 5% glucose solution.[54] Long term maintenance therapy requires the use of an indwelling venous catheter.

Foscarnet was found to be equivalent to intravenous ganciclovir for initial induction and maintenance of HIV-associated CMV retinitis when compared in the Studies of Ocular Complication of AIDS (SOCA) research trial.[29] In this and other studies, the median time to progression of retinitis on foscarnet maintenance therapy is 53 to 93 days. In the SOCA trial, patients randomised to foscarnet had better survival, with a mean of 12.6 versus 8.5 months, possibly related to the increased antiretroviral activity of the drug or to less myelosuppression allowing patients to remain on other antiretroviral drugs, such as azidothymidine.[29] This reported advantage[29,55] should be a minor factor in determining the agent for optimal therapy, especially today, given the wide range of potent antiretroviral therapies that are available. Maintenance doses of foscarnet of 120 mg/day may be more effective, with a median time to progression of 95 days or 31 days.[56] This higher dose, however, may also have more significant adverse effects.

An independent study showed that increasing area under the concentration-time curve of foscarnet significantly increases the time to progression of retinitis.[57] Foscarnet has also been demonstrated to have activity against ganciclovir-resistant strains.[49]

3.1 Common Adverse Reactions

3.1.1 Nephrotoxicity

Nephrotoxicity is the most frequently reported major adverse effect associated with foscarnet therapy.[49-53,56-58] Increases in serum creatinine level 2 to 3 times above baseline have been reported in 29 to 60%, and dose-limiting nephrotoxicity in 17 to 23%, of patients. Foscarnet should not be administered to patients with baseline serum creatinine clearance <0.9 L/h or those with serum creatinine level greater than 168 μmol/L. Although the nephrotoxicity is reversible with drug discontinuation, increases in serum creatinine level can be significant and may result in acute renal failure requiring temporary dialysis. The renal damage is primarily a consequence of acute tubular necrosis.

Hydration with normal saline 500ml to 2 L/day helps prevent the renal dysfunction.[59] Increases in serum creatinine level and peak serum creatinine level occur less often in hydrated patients (13 *vs* 66%). In a small study, oral hydration with 1.7L of fluid was found to be as effective as intravenous hydration.[60] Serum creatinine level should be measured twice weekly during induction and weekly during maintenance and dosage should be adjusted according to creatinine clearance. The mechanism by which hydration decreases the nephrotoxicity on clearing may include an increase in nephrotoxin clearance and inhibition of tubuloglomerular feedback abnormalities. Nephrogenic diabetes insipidus has also been associated with the use of foscarnet, although the mechanism is unclear.[61] It does appear to be reversible with discontinuation of the drug.

3.1.2 Electrolyte Abnormalities

Electrolyte abnormalities are commonly seen during foscarnet use and can include hypocalcaemia (15 to 35%), hypomagnesaemia (2 to 44%), hyperphosphataemia (25 to 90%), hypokalaemia (4 to 10%) and hypophosphataemia (12 to 13%).[51-53,56,62-64] These electrolyte abnormalities are potentially serious and if left untreated could result in neurological, cardiovascular or musculoskeletal sequelae. One study has shown prevention of these abnormalities by pretreatment with electrolyte solution.[65] While the total serum calcium level is usually normal, decreases in ionised calcium can be observed.[64] Although the mechanism is unclear, it is thought to be related to chelation of calcium by foscarnet. Undetected decreases in ionised calcium could result in perioral numbness, paraesthesia, arrhthymia, changes in levels of consciousness or seizures. One case of fatal hypocalcaemia has been reported in a patient receiving concurrent intravenous pentamidine.[66] Increases in serum phosphate level are also very commonly observed and are typically benign and self-limited. The mechanism is unclear and may be attributable to displacement of phosphate in bone by foscarnet. Because of these electrolyte abnormalities, patients require regular evaluation of their total and ionised calcium, phosphate, magnesium and potassium at least twice weekly during induction and weekly on maintenance therapy. Oral or intravenous electrolyte replacement should take place as the abnormalities arise rather than waiting until symptoms occur.

3.1.3 Haematological Abnormalities

Decreases in haemoglobin <8 g/L (20 to 50%) and granulocytes < 750/mm^3 (17 to 47%) are frequently reported.[29,50,51,53,56,62] Although clearly related to foscarnet in many cases, the contribution of other concurrent medications is often difficult to discern. As with ganciclovir, the use of colony stimulating factors may reverse the neutropenia and the anaemia typically responds to transfusion.

3.1.4 Central Nervous System Effects

Paraesthesias involving the extremities and perioral areas are reported in 4 to 20% of patients. The percentage of these events which is attributable to a decrease in ionised calcium is unclear. Seizures have been reported in 4 to 13% of patients, although the contribution of the drug is unclear as coexistent central nervous system opportunistic infections and malignancies have been present in most of the cases.[18,53,56] Other CNS effects associated with foscarnet have included tremor, anxiety, fatigue, irritability, hallucinations and headaches.

3.1.5 Thrombophlebitis

Thrombophlebitis is a common event following peripheral administration of the drug and can be decreased by dilution or by the administration of foscarnet through a central venous catheter.[54]

3.1.6 Gastrointestinal Events

Nausea, vomiting, anorexia, and malaise are frequently described adverse reactions related to infusion of foscarnet and have been reported in 28 to 56% of patients.[50-53,62] These subjective adverse effects appear to be dose-related as they are increased during induction courses, and they are the most frequent dose-limiting adverse effects. The use of antiemetics, or slowing the infusion rate may decrease the symptoms.

3.1.7 Mucosal Ulcers

Painful genital ulcerations or erosions on the glans of the penis or the vulval area have been reported in 5 to 28% of patients on foscarnet.[29,67-75] Occasionally, there has been intense erythema without ulceration or erosion. These events typically occur within 2 to 4 weeks of initiation of therapy and are reversible within 4 weeks of discontinuation of the drug. They may recur within days of rechallenge. On histopathology, ulceration and necrosis with endothelial swelling and a mixed infiltrate of granulocytes, lymphocytes and plasma cells have been observed. The ulcerations are thought to be caused by acute irritation by high urinary concentrations of foscarnet on the genital mucosa. The ulcerations are seen more commonly in uncircumcised men, which suggests that they may relate to drug retention in the subprepucial space. Mouth ulcerations have also been reported but it is unclear whether foscarnet is excreted in

saliva. It is recommended that patients be kept well hydrated to increase the frequency of urination and thereby regularly cleanse the genital mucosa. Some patients have obtained relief with topical corticosteroids or with barrier preparations, like petroleum jelly. Other patients have found no response with oral thalidomide, aciclovir or hydrocortisone cream.

Overall, adverse effects appear to be more frequent with foscarnet than with ganciclovir. In the SOCA trial, 6% of patients switched from ganciclovir to foscarnet because of an adverse event, while 36% switched from foscarnet to ganciclovir.[29]

4. Combination Intravenous Ganciclovir and Intravenous Foscarnet

While ganciclovir and foscarnet are equally effective in the control of CMV retinitis, nearly all patients with uncontrolled HIV replication will experience a relapse despite maintenance therapy. Although early relapses tend to respond to reinduction with the same or an alternative drug, the mean time between relapse shortens progressively and is associated with progressive loss of visual acuity. *In vitro* studies have shown that ganciclovir and foscarnet synergistically inhibit CMV replication.[76] Clinical studies have also shown efficacy of the combination.[77-79]

The CMV retreatment trial of the SOCA group demonstrated that for patients with persistently active or relapsed retinitis, the combination of standard dosages of ganciclovir and foscarnet was superior to either high dose foscarnet (120 mg/kg/day) or ganciclovir (10 mg/kg/day). The median time to progression of retinitis was 129 days for combination therapy versus 39 days for patients on foscarnet and 60 days for patients assigned to ganciclovir.[80]

4.1 Common Adverse Reactions

The incidence of anaemia, neutropenia, thrombocytopenia and nephrotoxicity was not statistically different between the 3 treatment groups. Use of GM-CSF to maintain neutrophil counts was common, ranging from 67 to 76% of patients in the various treatment arms.[80] Despite the fact that the incidence of toxicity was not felt to be different, patients receiving monotherapy were more likely to change treatment because of progression of the retinitis (42 to 70% versus 0%) whereas patients on combination therapy were more likely to switch because of toxicity (57 *vs* 0 to 7%), suggesting that the adverse effects associated with combination therapy were less well tolerated. Combination therapy did have a greater negative impact on quality of life of patients, primarily related to infusion times.

4.2 Central Venous Catheter Complications

Use of either intravenous ganciclovir, foscarnet or both requires the insertion of an indwelling central venous catheter for long term drug administration. Many patients find the catheter cosmetically unacceptable, as well as interfering with certain lifestyle activities such as workouts at the gym or swimming. The idea of foreign material extending out of the chest wall can have a major psychological impact. Insertion of the line itself can either be done in radiology under fluoroscopy (Hickman Line) or under local anaesthetic in the operating room (Portacath Line). Some patients prefer the Portacath, as they have the opportunity to be 'unhooked' at desired times. The insertion procedure can be complicated by pneumothorax, arterial puncture, or tunnel haematoma. The major line-associated problem is infection which may present either at the insertion site, along the tunnel or as a bacteraemia. The rate of infection in patients with HIV and CMV infection appears to be similar to that in patient groups with similar catheters inserted for other indications and ranges from 0.2 to 0.5 per 100 catheter-days.[81-87]

5. Intravenous Cidofovir

Cidofovir has a long, intracellular half-life (24 to 65 hours) which may explain its prolonged antiviral effects, and enables an intermittent treatment regimen which is more convenient and obviates the need for long term use of indwelling catheters. The

efficacy of cidofovir appears similar to that of ganciclovir or foscarnet, although no comparative trials have been performed. In newly diagnosed peripheral CMV retinitis, the median time to first progression as determined by retinal photographs is 64 to 120 days.[88] For patients with relapsed CMV retinitis, the time to next progression is 115 days, but this is reduced to a median of 49 days for patients receiving a reduced maintenance dosage of 3 mg/kg every 2 weeks.[89]

5.1 Common Adverse Reactions

5.1.1 Nephrotoxicity

Dose-related nephrotoxicity is the most important and potentially irreversible toxicity of this compound and is reported to occur in up to 50% of patients.[90] Cidofovir is concentrated by active transport into the proximal convoluted kidney tubular cells by an anion transporter in the basal lateral membrane. Efflux at the luminal membrane is slower than uptake, resulting in an increased concentration of drug in the proximal tubular cells. This may result in the observed dose-dependent renal toxicity which pathologically is characterised by degenerative necrosis of the proximal convoluted renal tubular cells.

Proteinuria is an early indicator of toxicity. If the toxicity continues, other evidence of proximal tubular cellular injury with loss of glucose, phosphate, uric acid and bicarbonate in the urine, and later, rises in serum creatinine level are observed.

The risk of nephrotoxicity can be decreased by prehydration with intravenous saline (1 to 2L) and by the use of probenecid.[90] Probenecid, a uricosuric agent, is an inhibitor of organic anion transport which competes with cidofovir for uptake in the proximal tubular cells. It is given as 2g orally 3 hours prior to, and then 1g at 2 and 8 hours after, each cidofovir infusion. Adverse reactions occur commonly to the probenecid. Constitutional symptoms such as fatigue, nausea, malaise, headache, dyspepsia and flushing occur in 50 to 60% of patients and are dose limiting in up to 7%.[88,89] A hypersensitivity reaction characterised by rash, pruritus and fever has been described. This reaction is frequently delayed, appearing 4 to 6 hours after administration and typically does not occur until after the third dose. Probenecid is a benzoic acid derivative with a sulfa moiety, and is contraindicated in patients with a history of severe hypersensitivity reactions to either probenecid or other sulfa-containing medications. Dyspepsia can be decreased by administration of the drug with food. Pretreatment with antiemetics, antihistamines and/or paracetamol (acetaminophen) is frequently helpful in decreasing the frequency or severity of adverse reactions.

In controlled trials of cidofovir, the risk of nephrotoxicity has been decreased by use of saline hydration and probenecid, with proteinuria (2+ or greater) reported in 14 to 18% and increases in serum creatinine level (increases by 177 to 265 μmol/L) in 5 to 12% of patients.[88,89] It is unclear if the risk of nephrotoxicity increases over time. Careful monitoring is required because the nephrotoxicity is not always completely reversible and because one case of fatal metabolic acidosis has been reported. Prior to each dose, serum creatinine level should be measured and quantitative urine evaluation for protein should be performed. Cidofovir is contraindicated if the creatinine level is >124 μmol/L, the creatinine clearance is <3.3 L/h or if there is 2+ or greater proteinuria (>1 g/L). At the earliest signs of nephrotoxicity (for example proteinuria >2+ or creatinine level increasing 27 to 35 μmol/L above baseline) the drug dosage should be decreased, (i.e. 5 mg/kg to 3 mg/kg every 2 weeks) or deferred. For more significant toxicity, i.e. proteinuria >3+ or creatinine level increasing more than 44 mmol/L above baseline, the drug should be discontinued.[11]

5.1.2 Other Adverse Reactions

Alopecia has been reported in 7% of patients receiving low dose cidofovir (3 mg/kg) and 25% receiving high dose cidofovir (5 mg/kg every 2 weeks) as maintenance therapy.

Iritis is a common adverse effect following intravitreous injection of cidofovir; this may also be observed less commonly with intravenous cidofovir exposure. 11 cases have been reported after

intravenous administration among 43 patients (26%).[91] Iritis usually occurred 5 days after the fourth cidofovir dose and was associated with decreased visual acuity. While the inflammation may be severe, it typically responds to topical corticosteroid therapy. Although cidofovir may be continued, recurrent inflammation or permanent hypotony may occur.[92] Hypotony has been reported in 3 to 12% of patients, often in association with iritis. Uveitis has also been reported in 4 to 7% of patients. Regular slit lamp examinations of the anterior chamber should be performed monthly or at least before each dose of cidofovir. This examination should also include measures of intraocular pressure. Cidofovir should be discontinued if the intraocular pressure decreases to a value <50% of the baseline.

Neutropenia (absolute neutrophil count <750/mm^3) has been reported in 15 to 30% of patients. Routine haematology tests should precede each dose of drug.

In animal studies, cidofovir is carcinogenic, teratogenic and causes hypospermia and thus it should be considered a potential carcinogen in humans. Women of childbearing potential should use effective contraception during treatment and the drug should not be used in pregnancy. Men should be advised to use barrier contraception.[11]

6. Intravitreal Drug Administration

Achieving inhibitory antiviral concentrations in the vitreous fluid of the eye may play an important role in the successful suppression of retinal CMV replication. This is supported by the observation that patients with relapsed retinitis often respond to reinduction therapy with the same medication. With direct administration of drug into the eye, achievable local concentrations may be much higher, because of the small volume of the vitreous fluid, and longer elimination half-life.[34] Therefore, infrequent intraocular drug administration or intraocular implants of ganciclovir may be an option for patients with immediate sight–threatening disease, in combination with systemic therapy to achieve greater control of active retinitis, for those patients unable to tolerate systemic antiviral therapy, or who will not consent to an indwelling intravenous catheter.

6.1 Intraocular Ganciclovir Implant

A sustained high release intraocular ganciclovir implant has been developed. The surgically implanted device releases a constant amount of ganciclovir (1 μg/h) into the eye over 6 to 8 months. While implants are convenient, they are also expensive [approximately $5000 (1999 Canadian dollars; $US3500) per implant]. In randomised, controlled trials, the implant alone has been shown to be substantially more effective than intravenous ganciclovir, delaying the progression of CMV retinitis for over 200 days (a time period virtually equal to the duration the device continues to release drug)[93,94] compared with 60 to 70 days.[29]

6.1.1 Contralateral and Extraocular Cytomegalovirus Disease

Because CMV retinitis is part of a systemic disease and haematogenous dissemination is thought to be central in its pathogenesis, systemic antiviral therapy is warranted in addition to the ganciclovir implant to prevent the development of extraocular disease.[95] The incidence of retinitis developing in the contralateral eye in patients treated with an implant alone has been reported to range from 29 to 67% at median times of 87 to 203 days.[93,96,97] Extraocular CMV disease (gastrointestinal, neurological or pulmonary) occurs in 11 to 32% of patients.[93,96,97]

Martin et al.[98] have demonstrated that the addition of oral ganciclovir 4.5 g/day decreased the incidence of contralateral CMV retinitis from 37.8 to 22.4% compared with an implant alone, and decreased the incidence of extraocular disease ($p = 0.018$) at 6 months. Progression of CMV retinitis in the implanted eye was also delayed by concomitant oral ganciclovir.

Because of these benefits it is now recommended that patients receive oral ganciclovir at a dose of 1 to 1.5g 3 times daily in conjunction with the intraocular implants.[46,99]

6.1.2 Ocular Adverse Events

Most patients experience an immediate but temporary reduction in functional visual acuity secondary to the implant procedure, with return to baseline by 28 days.[93,94] In randomised trials, a vision compromising event occurred in approximately 10% of the patients who received implants.[93,94] Such complications include severe postoperative corticosteroid-responsive inflammation[93] and transient postoperative diffuse vitreous cavity haemorrhage.[93,94] The risk of haemorrhage may be higher in eyes receiving a subsequent implant compared with those receiving a primary implant.[93] Endophthalmitis occurs infrequently, at an incidence of approximately 1 to 3%,[94,96,97] and may rarely lead to permanent loss of vision.[94]

6.1.3 Retinal Detachment

The early literature reports an 11 to 18% risk of retinal detachment, occurring 6 to 20 weeks after surgical implantation of ganciclovir.[93,96,97] These rates are similar to the 13 to 26% incidence of retinal detachment observed in patients treated with intravenous ganciclovir.[100,101] However, in the latter group, the median time to development of retinal detachment was approximately 120 days.[100] In surgical associated cases, retinal detachment may coincide with the development of posterior vitreous separation and retinal tears along the border of healed retinitis. Patients with extensive lesions in the anterior retina may be at higher risk. Thus, while the overall risk of retinal detachment appeared to be similar in patients treated with either intravenous or intraocular ganciclovir, the time to development of retinal detachment may be shorter in eyes receiving an implant. Recent reports suggest the incidence is not increased and may relate to surgical experience.[94] The implant is depleted of drug after 5 to 8 months, which may necessitate replacement with the risk of additional complications. The outcome of undergoing repeated implantation procedures is not known.

6.2 Intravitreal Ganciclovir Injection

Successful short term results have been observed with intravitreal ganciclovir injections of 200μg administered through a small gauge needle every 2 to 3 days for induction, and then weekly for maintenance therapy of CMV retinitis.[102-105] Data on long term use (i.e. 8 to 14 months) in small numbers of patients suggest that this route of administration may be as effective as systemic maintenance therapy.[106-108] However, the lack of systemic therapy may place the patient at increased risk for contralateral eye or extraocular CMV infection.[93,94]

6.2.1 Contralateral and Extraocular Cytomegalovirus Disease

Contralateral retinitis is reported in 10 to 30%[106,108] and extraocular CMV disease in 16% of patients not receiving concurrent systemic therapy.[106]

6.2.2 Adverse Ocular Reactions

The maximally tolerated intravitreal dose in humans has not yet been established. A transient increase in intraocular pressure is frequently observed, which may result in intense ocular pain for approximately 30 minutes, or even total amaurosis (by interruption of retinal vascular flow) for 1 to 10 minutes after injection. Other potential complications of intravitreal ganciclovir that have been reported include lens damage, subconjunctival haemorrhage, keratitis, corneal ulceration, optic nerve atrophy, and retinal detachment.[109] Little is known about the rate of complications associated with repeated intravitreal injections.

In a prospective series of 44 patients (64 eyes), a total of 710 injections (400μg each), or 11 injections per eye (range 2 to 49) were administered over a mean of 9 weeks.[106] Ocular pain of variable intensity was reported; this usually disappeared within 30 minutes but increased with the number of successive injections. A degree of scleral induration developed in the area of injection, and subconjunctival haemorrhages were frequent. Retinal detachment occurred in 5 eyes, and intravitreal haemorrhages were noted in 2 patients with low platelet counts. Keratitis occurred in 5 eyes (8%), and was associated with the intensive use of anaesthetic drops. Optic disc atrophy occurred in 5 eyes. Intraocular pressure was measured for the first 24

eyes, and showed an immediate increase postinjection, decreasing to baseline within 5 minutes. No cases of infection or cataract were observed.[106]

6.3 Intravitreal Foscarnet Injections

Reported literature describing experience with intravitreal foscarnet injections is limited. Use of 1200μg (0.05ml) doses per injection has primarily been described in case reports and series for salvage therapy in patients unwilling or unable to tolerate systemic therapy.[29,110,111] A prospective open study of high dose intravitreal foscarnet (2400μg) was conducted in 11 patients (15 infected eyes).[112] The induction regimen comprised 6 injections at 72-hour intervals during the first 18 days. Maintenance therapy consisted of weekly injections of 2400μg indefinitely. Patients were instructed to administer topical tobramycin and povidone iodine eyedrops 2 days before and after each injection. Patients were followed for a mean of 16 weeks, and a total of 304 injections were given. No intraocular complications, including retinal detachment, intravitreal haemorrhage, endophthalmitis, or cataract, were observed.[112]

Foscarnet intravitreal injections appear to be well tolerated. It is assumed that the frequency of complications would be similar to that of intravitreal ganciclovir. Some investigators and clinicians have suggested that intraocular foscarnet may have additional advantages over ganciclovir.[12] For instance, foscarnet may be administered in a smaller amount of liquid (0.05 *vs* 0.1ml), which may potentially be associated with a lower risk of affecting central retinal artery circulation and reflux of liquid, thus possibly reducing the occurrence or severity of transient amaurosis and increased intraocular pressure. Also, the pH of foscarnet solution is more physiological compared with ganciclovir solution (7.4 *vs* 10.1), and could therefore be less irritating to the vitreous fluid.[112] Finally, foscarnet is also active against HIV and may therefore be effective against other ocular manifestations of HIV infection, such as iridocyclitis and retinal dysfunction. However, the clinical significance of these postulated advantages is unclear. Experience with intravitreal injections has been quite limited, with small numbers of patients in uncontrolled situations, with short follow-up periods, and no comparative trials between the 2 agents for efficacy or toxicity have been conducted.

6.4 Intravitreal Cidofovir

Cidofovir diphosphate has a long intracellular half-life (17 to 30 hours), which allows for infrequent administration. In phase I/II and II/III studies of single intraocular injections of cidofovir 20μg (0.1 ml), the median time to retinitis progression ranged from 55 to 64 days.[113,114] In a prospective, nonrandomised case series, intravitreal cidofovir injections were administered as maintenance therapy every 5 to 6 weeks with little or no progression during the study period (mean follow-up of 15 weeks, range 0 to 58).[115] Although the convenience of the infrequent administration schedule is appealing, the unacceptably high incidence of adverse ocular effects has led investigators and the manufacturer to recommend that cidofovir no longer be administered via the intravitreal route.

6.4.1 Adverse Ocular Reactions

Hypotony

Hypotony may occur secondary to direct damaging effects of cidofovir to the nonpigmented epithelium, the inner vasculature of the pars plicata, or both, resulting in decreased production of aqueous humour.[114,116] Use of concomitant probenecid may reduce the incidence and severity of ocular hypotony secondary to cidofovir. In a phase I/II study, clinically significant hypotony was observed in patients receiving high dose intravitreal cidofovir.[114] In a large study, intraocular pressure was measured prospectively in 63 patients (97 eyes) who received a total of 229 intravitreal cidofovir injections.[116] All patients received concomitant oral probenecid. After the first intravitreal injection, the mean intraocular pressure was lower by 2.2mm Hg at 2 to 3 weeks and by 1.3mm Hg at 5 to 6 weeks compared with baseline ($p < 0.001$ and $p = 0.0025$, respectively). An addi-

tional decrease at 2 to 3 weeks and 5 to 6 weeks was observed after the second injection. Eyes that experienced uveitis had greater mean drops in intraocular pressure compared with eyes that did not develop uveitis (mean 5.2mm Hg versus 1.5mm Hg; $p < 0.0001$). One patient in this series (1%) developed severe irreversible hypotony (intraocular pressure of 0mm Hg) with irreversible visual loss 1 week after the second injection.[116]

Uveitis

Administration of intravitreal cidofovir was noted to be associated with a 14 to 32% risk of mild to moderate iritis.[113,115,117,118] Iritis usually occurred anterior to the lens-iris diaphragm, and was associated with nongranulomatous keratitic precipitates and, occasionally, posterior synechiae. Symptoms included mild pain, photophobia, and visual blurring within the first 2 weeks after a cidofovir injection. All cases of iritis resolved within 2 weeks, with administration of topical steroids and cycloplegia. No long term adverse visual effects were noted in some studies.[113,118] Others noted that long term sequelae of synechia and cataract developed in 19 and 11% of patients, respectively.[119] Patients who developed iritis after an initial injection were more likely to develop a second episode of iritis in the same eye following a subsequent injection ($p = 0.015$).[118]

7. Drugs in Development

7.1 Valganciclovir (Ganciclovir Valine Hydrochloride)

Valganciclovir is a valyl ester prodrug of ganciclovir. It is rapidly converted into ganciclovir following de-esterification as it is absorbed through the intestinal wall. The oral bioavailability is much improved over oral ganciclovir and estimated to be 60%.[120] Phase I pharmacokinetic studies show the profile to be very similar to that observed with the intravenous formulation, although the peak C_{max} is slightly lower following a single 450mg oral dose, at 3.3 mg/L. Absorption is also increased by taking the medication with food.[120] Valganciclovir is being evaluated as both induction (900mg twice daily) and maintenance therapy (900mg once daily) of CMV retinitis. The toxicity profile is similar to that of ganciclovir, and to date no unexpected toxicities have been observed. If the clinical trials prove it to be equivalent to the intravenous formulation of ganciclovir it will likely replace the latter drug. An oral formulation obviates the need for an indwelling catheter, and the greater bioavailability and fewer number of tablets to be taken each day are clear advantages over the previous oral formulation.

7.2 Adefovir Dipivoxil

Adefovir dipivoxil, also known as bis-POM PMEA, 9-[2-(bispivaloyloxymethyl phosphonyl methoxyethyl] adenine, or GS 840, is an investigational prodrug of adefovir (PMEA), a nucleotide analogue. Because of its intracellular half-life of 17 hours,[121] adefovir dipivoxil may be administered once daily. Adefovir has been shown to have inhibitory activity against HIV, and other viruses including CMV, including some ganciclovir- and foscarnet-resistant strains. It demonstrates additive activity with ganciclovir, foscarnet, or cidofovir.[122] Clinical experience with adefovir for the management of CMV disease is extremely limited. It is being evaluated as a prophylactic agent.

In animal studies, renal damage was the dose-limiting toxicity observed. In human studies, all cases of elevated serum creatinine level have occurred after at least 6 months of therapy, appear to be dose-related and all were reversible upon drug discontinuation. Other events observed include tubular toxicity with urinary losses of phosphate, bicarbonate, and glucose. Although reversible, they have been observed in up to 40% of patients after 48 weeks of treatment.[123] The dosage of adefovir should be adjusted for renal impairment. In phase I/II studies, the other primary adverse effects have included dose-related, mild-to-moderate gastrointestinal complaints, including nausea, vomiting, and diarrhoea, asthenia, transient neutropenia, and moderate increases in hepatic transaminase levels.[124,125]

Depletion of L-carnitine levels has been observed. After 14 days' administration, serum carnitine levels decreased by 42 to 66% from baseline in patients treated with adefovir 125 to 500mg.[124,125] Although no patient experienced clinical signs or symptoms suggesting carnitine deficiency, such as myopathy or encephalopathy, the manufacturer has recommended oral supplementation with L-carnitine 500 mg/day. After discontinuation of adefovir, serum carnitine levels returned to normal.

7.3 Lobucavir

Lobucavir is a nucleoside analogue with activity against a wide range of herpes-type viruses.[126] It is well tolerated at single doses of up to 800 mg/day and is 40% bioavailable.[127] At steady-state doses of 200 to 400mg four times daily, the area under the concentration-time curve exceeds the effective dose to inhibit 50% of strains of CMV.[127]

In asymptomatic shedders of CMV, lobucavir has been demonstrated to eradicate viruria and reduce the CMV titre in semen. No dose-related clinical or laboratory adverse events have been demonstrated.[128]

7.4 Benzimidazole

This drug is targeted at UL89, the most highly conserved open reading frame in the herpes viruses.[129] In phase I/II trials it has been shown to have antiCMV activity in asymptomatic urine and semen shedders and good tolerability and pharmacokinetic profiles.[130] The most commonly reported adverse effects include taste disturbance, headache, fatigue, nausea and diarrhoea.[130,131]

7.5 Intravitreal Fomivirsen

Fomivirsen sodium, also known as ISIS 2922, is an investigational phosphorothioate antisense oligonucleotide. Antisense oligonucleotides bind to the sense strand of viral messenger RNA (mRNA) with a high degree of specificity, and prevent translation of mRNA into protein, thereby inhibiting viral replication.[132] Fomivirsen is a highly selective and potent antisense compound complementary to the major immediate early region of human CMV mRNA.[133] It has additive antiCMV activity to ganciclovir and foscarnet, and is active against strains of CMV that have developed resistance to other antiviral agents.[134] It is currently being evaluated in phase III trials for the treatment of CMV retinitis in patients with AIDS.[133,135] At the present time, intravitreal fomivirsen is indicated as an alternative agent for secondary prophylaxis of CMV retinitis.[46] The usual dose is one vial injected into the vitreous, repeated every 2 to 4 weeks as indicated.

7.5.1 Adverse Events

In dose-ranging studies, reversible ocular inflammation of the posterior and anterior chambers frequently occurred between the second and third injections.[133,136] Posterior chamber inflammation generally resolved with time and continued administration, while inflammation of the anterior chamber responded to topical corticosteroid therapy. Transient increased intraocular pressure has also been observed.[135] No patients discontinued therapy due to drug-related ocular adverse effects.[135] High doses have been associated with retinal pigment epithelial stippling, and decreased peripheral vision.

8. Cytomegalovirus Therapy in the Highly Active Antiretroviral Therapy Era

Over the past few years, improved survival, decreased rates of hospitalisation, and decreased incidence of opportunistic infections and malignancy have been reported for patients living with HIV.[137-140] These dramatic changes in outcome have been associated with the use of combination highly active antiretroviral therapy, especially regimens containing the protease inhibitor class of compounds.[138,139] The degree to which the functional repertoire of the immune system can be reconstituted by potent antiretroviral therapy remains under study, however, the changes noted above attest to the fact that some immune restoration must occur.

Since the widespread use of highly active antiretroviral therapy the incidence of CMV retinitis

has decreased dramatically. Baril et al. [3] were the first to report that the incidence of CMV disease in their French centre decreased from 18.7 first episodes per 100 person-years in the period January 1995 to June 1996, to 5 per 100 person-years in the period July to December 1996. Brodt et al.[4] reported a decline in the incidence of CMV retinitis from 14.7 cases per 100 person-years in 1992 to 3.6 per 100 person years in 1996 in the Frankfurt AIDS Cohort Study. Moore et al.[5] reported that the use of combination antiretroviral therapy in 1996 to 1997 was associated with a relative risk of CMV disease of 0.21 compared with the years 1993 to 1995.

Additionally, the population at risk for CMV retinitis has changed. Cases of CMV retinitis have been reported at CD4+ cell counts higher than seen in the past and frequently within a few weeks of the initiation of highly active antiretroviral therapy.[2] It has been hypothesised that these patients have subclinical, or symptomless CMV retinal infection which progresses to symptomatic disease by an improvement in CMV-specific immunity resulting from highly active antiretroviral therapy.

Time to death from the first diagnosis of CMV retinitis has also increased. Walsh et al.[6] reported that the median survival in their cohort before December 1995 was 256 days. As of May 1996, the median survival for the entire group of patients had risen to 720 days. For those who took no further antiretroviral therapy the mean survival was 224 days, compared with 353 days in those who took nucleoside reverse transcriptase inhibitors, and 914 days in those who took a protease inhibitor. Lifelong therapy for CMV retinitis, therefore, takes on new meaning in the highly active antiretroviral therapy era. Consequently, more patients and their physicians are choosing oral ganciclovir or intraocular injections as maintenance therapy, avoiding the long term venous access devices.

Coincident with the decreasing incidence of CMV retinitis and improved survival following diagnosis of CMV, the clinical presentation has also changed. Patients presenting with new CMV retinitis while receiving highly active antiretroviral therapy have a granular, greyish, less intense infiltrate. Progressions also occur less frequently, and with less intensity, suggesting that a modification of the history of treated disease has occurred. Reactivations are more frequently described as smouldering of the borders rather than advancements, although without treatment these can still cause further retinal destruction and necrosis. The incidence of and time to progression have also changed. In one series,[141] 11 relapses were noted in 63 patients who received antiretroviral therapy which contained a protease inhibitor, at a mean of 1326 days. This was contrasted to 25 relapses at a mean of 182 days in 46 patients who did not receive a protease inhibitor. Therefore, the current management of CMV retinitis includes the initiation of antiretroviral therapy in those who have not previously received it, or a change or intensification of therapy in patient in whom CMV retinitis develops with inadequate control of HIV replication.

The observations on the ability to control reactivation or development of CMV retinitis without specific antiCMV treatment suggests that a T cell–mediated response confers protection against CMV and that partial immune recovery is possible, even at late stages of AIDS, despite high levels of HIV replication.[142] Based on these observations, investigators have attempted to discontinue CMV maintenance therapy in selected HIV-infected patients. Whitcup and colleagues[7] described 4 patients who experienced rises in CD4+ counts in response to highly active antiretroviral therapy and had extended intervals free of CMV retinitis progression without specific antiCMV maintenance therapy. Macdonald et al.[8] discontinued maintenance therapy in 11 patients with healed retinitis, who had absolute increases in their CD4+ counts on highly active antiretroviral therapy. Of these patients, 3 were in a study of intraocular cidofovir and were noted to remain stable without maintenance therapy. At the time of discontinuation of maintenance therapy, the median CD4+ count was 183/mm^3 (range 63 to 406) as compared with 42/mm^3 at the time of the CMV diagnosis. When maintenance therapy was discontinued the median

viral load was 3.95 log copies/ml but was below the level of detection of the assay for only 3 out of 11 patients. Most patients had experienced a 1 log reduction in viral load since starting highly active antiretroviral therapy, but this was not always sustained. No patient had a progression of CMV retinitis after a mean of 156 days follow up (range 92 to 558 days). Despite detectable viral loads in 8/11 patients, the CD4+ count remained elevated in all patients, with a mean of 223/mm^3 (range 44 to 507) at last visit.

Tural et al.[9] discontinued maintenance therapy in 7 HIV patients with CMV retinitis. All patients were on highly active antiretroviral therapy and had a CD4+ count >150 cells/mm^3, undetectable HIV viral loads, and a negative quantitative polymerase chain reaction assay for CMV. After a median follow-up of 9 months (range 9 to 12 months), no evidence of relapse of CMV retinitis had occurred. All patients continued to have increased CD4+ counts, low viral loads (<200 copies/ml) and negative assays for CMV viraemia.

These reports have led many investigators to discontinue maintenance therapy in patients with stable CMV retinitis. However, much remains uncertain. The efficacy of such a manoeuvre is unknown, given the small number of patients reported to date. The improvement in lifestyle, decreased risk of catheter-associated infection, decreased incidence of drug-associated adverse effects, and selection pressure for resistant CMV isolates must be balanced against the risk of progression of CMV retinitis and potential visual loss or risk of extraocular CMV disease which is less amenable to therapy. The patient parameters that should be met for considering discontinuation of maintenance therapy are unclear. For example is there a minimum CD4+ count, maximum viral load, duration of previous remission of CMV or other important criteria that should be met before therapy can be discontinued? These issues are briefly discussed in the 1999 Draft Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus. The guidelines suggest that discontinuation of chronic maintenance therapy may be considered if the following conditions apply: the patient has sustained (>3 to 6 months) increases in CD4+ cell counts of at least 100 to 150 cells/mm^3, the retinitis is not in an immediately sight-threatening area (i.e. not zone 1 disease), there is adequate vision remaining in the contralateral eye, the patient does not have manifestations of extraocular CMV disease and regular ophthalmic monitoring can be done.

If the patient meets all the aforementioned criteria, then the decision to suspend maintenance therapy may be made in consultation with an ophthalmologist experienced in the management of HIV disease and CMV retinitis.

Similarly, there are no data available yet to guide the reinstitution of maintenance therapy if a patient's HIV disease status changes. It may be reasonable to reinititate maintenance antiviral therapy when a patient is no longer responding virologically and immunologically to highly active antiretroviral therapy. In such cases, anti-CMV therapy may be restarted once the patient's CD4+ cell count drops to below 50 to 100 cells/μl.[46,99] Research protocols are currently underway in many centres to further clarify these issues.

9. Conclusions

This review outlines the various treatment options for CMV retinitis complicating HIV infection. We have focused on the common adverse events associated with each of the available agents and have discussed ways to manage them. When choosing therapy for a patient with CMV retinitis these adverse reactions must be considered. For a patient with baseline haematological toxicity use of either systemic foscarnet or cidofovir, or the ganciclovir implant would be most appropriate. For a patient with baseline nephrotoxicity, ganciclovir would be the agent of choice.

Over time, and despite maintenance therapies, relapses of retinitis commonly occur. With the emergence of drug-resistant virus, it often becomes necessary to switch to an alternative agent despite the potential toxicity. In this setting it is important

to monitor closely for the adverse events, to respond to them quickly, to modify doses as appropriate (i.e. for renal toxicity) or to use supportive therapy such as fluid and electrolyte replenishment with foscarnet, saline hydration and probenecid with cidofovir, and transfusions or growth factors for the haematological toxicity of ganciclovir. Intraocular injections of medication can be used as adjunctive therapy for those patients in whom full doses of systemic therapy cannot be tolerated, or to supplement systemic therapy in attempts to achieve higher local drug concentrations and better control of active retinitis.

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