Cytomegalovirus Infection of the Central Nervous System

Paul Griffiths, Department of Virology, Royal Free and University College Medical School, London, UK.

KEY WORDS:
CYTOMEGALOVIRUS ▮ CENTRAL NERVOUS SYSTEM ▮ ENCEPHALITIS ▮ GUILLAIN-BARRÉ SYNDROME ▮ THERAPY MANAGEMENT RECOMMENDATIONS

SUMMARY
Studies report that 40–100% of the general population are infected with cytomegalovirus (CMV), a virus associated with severe neurological conditions, such as CMV encephalitis, and which may have a role in some cases of Guillain-Barré syndrome. CMV infection is a particular concern among individuals with HIV, as almost all are co-infected with it. The introduction of highly active antiretroviral therapy (HAART) has provided a means of reconstituting the immune system of those with HIV/AIDS in such a way as to allow CMV infection to be controlled. In doing so, HAART has done much to reduce the mortality rate associated with CMV disease in such patients. Despite this, response to treatment in these patients remains suboptimal and many do not have access to such therapy, so, efforts to improve the treatment of CMV have been a priority. The *International Herpes Management Forum* (IHMF) has developed management guidelines to promote the improved diagnosis and treatment of CMV disease of the central nervous system (CNS). It is recommended that polymerase chain reaction (PCR) for viral DNA should be performed on CSF as a means of diagnosing CMV infection of the CNS. As CMV disease is always preceded by viraemia, treatment should be directed toward the prevention of CMV disease. However, if CMV disease develops, ganciclovir is recommended as therapy and continued in a maintenance fashion, which can be discontinued should CD4 count remain above 100 cells/mm³ for 6 months. In many circumstances, valganciclovir may be preferred, depending on the level of function in the patient, their ability to take oral therapy and the severity of disease. Use of foscarnet should be limited to ganciclovir-resistant cases due to the high level of toxicity associated with the drug and its intravenous mode of administration.

Introduction

BETWEEN 40% AND 100% of individuals in the general population are seropositive for cytomegalovirus (CMV). Furthermore, almost all homosexual men with HIV are co-infected with CMV.[1,2] CMV can infect the retina, gastrointestinal tract, liver, lung and nervous system.[3,4]

Highly active antiretroviral therapy (HAART) refers to a combination of three or more antiretroviral drugs from at least two antiretroviral drug classes. HAART suppresses viral replication and, in doing so, allows restoration of the CD4+ T-cell count and, consequently, a diminished risk of opportunistic infections, including CMV. In the pre-HAART era, reactivation of CMV was the most commonly encountered opportunistic infection in patients with AIDS and was associated with significant morbidity and mortality.[5] The prevalence of CMV disease in people with AIDS had risen to 45%, partly because prophylaxis and treatment of other AIDS-related opportunistic infections had improved survival.[6] With the advent of HAART, the rate of CMV disease in the USA declined from 15 cases per 100 person-years in 1994 to three cases per 100 person-years in 1995.[7]

This change in the prevalence of CMV disease, which is apparent in most countries where HAART is available, should be borne in mind when considering the frequency of complications. However, CMV disease remains a problem in untreated patients, such as those without access to HAART or who are poorly compliant with therapy, or who fail therapy. Moreover, the overall prevalence of HIV infection in the population is increasing and, consequently, the absolute number of cases of CMV disease will increase.

The most common manifestation of CMV disease is CMV retinitis, which accounts for 85% of all cases of CMV clinical syndromes.[5] Gastrointestinal disease is the next most common (15%), and includes oesophagitis, colitis, gastritis and hepatitis.[5] Clinical CMV disease of the nervous system accounts for less than 1% of all CMV diseases, although, as discussed below, this may well be underestimated.[4,8] Several CMV-related neurological complications have been described, including retinitis, encephalitis,[9] polyradiculomyelopathy[10–12] and neuropathy. It may also have a role in Guillain-Barré syndrome.[13,14] This publication considers the natural history, diagnosis and treatment of these diseases of the CNS.

CMV Infection of the Nervous System in Patients with HIV

- Research into the pathogenesis of CMV CNS disease is required as it may benefit management approaches (research need recommendation)

Cytomegalovirus localizes in the brain in patients with AIDS, where it can infect all cells in the brain, including astrocytes, neurons, oligodendroglia, cells of monocyte-macrophage lineage and capillary endothelia.[15] Although neuropathological studies have shown a clear association between neurological damage and clinical manifestations attributable to CMV, this is difficult to define *in vivo*. This is partly because HIV, like CMV, is also highly neurotropic, has frequently been found in the brain of patients with CMV encephalitis and is also capable of causing subacute or chronic encephalitis.[16,17] Moreover, other viruses may co-infect brain cells in patients with AIDS, producing multiple co-infections. For example, Epstein–Barr virus (EBV) has been associated with the development of primary CNS lymphoma, JC virus infection with progressive multifocal leukoencephalopathy and herpes simplex virus (HSV) with CMV-related neurological disease.[18]

Clinical Manifestations of CMV-related CNS Infection

CMV ENCEPHALITIS

Cytomegalovirus encephalitis is the major CMV-induced pathology of the nervous system in people with AIDS with a CD4+ cell count of less than 50 cells/mm³. It is assumed that patients will become at risk of developing CMV viraemia once the CD4+ cell count declines below 100 cells/mm.[3,19] The prognosis is poor, with death ensuing within weeks of diagnosis in untreated individuals.

At autopsy, the main neuropathological feature of CMV encephalitis is a ventriculo-encephalitis, which typically involves the periventricular areas where

RECOMMENDATIONS AND STATEMENTS

- CMV disease is always preceded by viraemia (although not always detectable unless frequent samples are collected). Therefore, therapy should be directed toward the prevention of CMV disease (category 1 recommendation)
- Diagnosis of CMV infection of the CNS should be performed using polymerase chain reaction (PCR) detection of viral DNA in the cerebrospinal fluid (CSF) (category 1 recommendation)
- HAART results in reduced risk of CMV disease and prolonged survival following CMV disease in patients with HIV/AIDS (category 1 recommendation)
- Ganciclovir is recommended for the therapy of CMV disease; maintenance therapy with ganciclovir can be discontinued if the CD4 count remains above 100 cells/mm^3 for 6 months (category 1 recommendation)
- Foscarnet should be reserved for treatment of ganciclovir-resistant CMV because of its toxicity and intravenous mode of administration (category 2 recommendation)
- Valganciclovir may be preferred to intravenous or oral ganciclovir under certain circumstances for the treatment of CMV encephalitis. The choice of agent will depend upon the level of function of the patient, their ability to take orally administered drugs and the severity of the disease (category 2 recommendation)
- Response to the treatment of established CMV disease (especially CNS disease) remains suboptimal. Every effort should, therefore, be made to prevent the array of CMV diseases by employing treatment strategies shown to be successful in immunocompromised allograft recipients (category 3 recommendation)
- Ganciclovir-resistant CMV is more common than has been appreciated in the past and the possibility of resistant CMV should be considered in cases of CMV encephalitis (category 3 recommendation)
- Patients not responding to ganciclovir therapy should be evaluated for the emergence of resistance using genotypic analyses (category 3 recommendation)
- Although there is a lack of data from randomized clinical trials, currently available data point to a clear lack of benefit from either ganciclovir or foscarnet therapy of CMV CNS disease (category 3 recommendation)
- Randomized, controlled trials are needed to define the therapeutic index (efficacy/safety) when existing or new drugs are used for prophylaxis or pre-emptive therapy of CMV CNS disease (research need recommendation)
- Even though patients with CMV-related CNS disease are few in number, better designed, randomized, controlled trials of treatment and management are required (research need recommendation)
- Research into the pathogenesis of CMV CNS disease is required as it may benefit management approaches (research need recommendation)
- The potential of long-term valganciclovir therapy to improve mortality and morbidity outcomes in immunocompromised children (e.g. those with HIV or transplant recipients) with CMV CNS disease needs to be assessed (research need recommendation)

RECOMMENDATION AND STATEMENT CATEGORIES

Category 1

Consistent evidence from controlled clinical trials. For example, for an antiviral, this would include results from at least one well-designed, randomized, controlled clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

Category 2

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3

Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need

Area in which research is warranted.

necrotic lesions can be found. There can also be focal necrosis deep in the parenchyma, some of which may not be associated with the periventricular lesions. Another finding is micronodular encephalitis, where microglial nodules are found in the parenchyma, cerebellum and spinal cord.[20] In some cases, the meninges may be involved.

Diagnosis of CMV encephalitis: In the pre-HAART era, it is likely that CMV disease was underdiagnosed. Although clinical CMV disease of the nervous system accounts for less than 1% of all CMV diseases in people with AIDS, post-mortem studies have detected CMV in the nervous system of 15–76% of people with AIDS.[4,8,21] For example, in an autopsy study of 213 deaths, 152 (71%) cases had evidence of CMV in the brain that was not diagnosed pre-mortem (Table 1).[21] Thus, a high degree of discordance exists between clinical diagnosis and post-mortem findings. While not all cases of undiagnosed CMV infection represent either rapidly progressive or fatal disease, evidence demonstrates that it can adversely affect patients. For example, when 16 patients with newly diagnosed CMV retinitis were compared with 32 age-matched controls, two thirds of the 16 were found to have neurological impairment, of which a third was attributed to CMV.[22] Magnetic resonance imaging (MRI) revealed that damage to the CNS was twice as frequent in those with retinitis.

The clinical features of the disease in patients with AIDS have not been completely identified;[4,23] however, the main neurological symptoms include drowsiness, fever, disorientation, confusion, apathy and signs associated with focal deficits such as seizures, changes in the sensorium and headache, along with cranial nerve deficits and the presence of gaze-directed nystagmus. The focal signs indicative of brainstem or cerebellar involvement are present in approximately 30% of CMV encephalitis cases, sometimes in association with Guillain-Barré syndrome or polyradiculomyelitis.[24] The onset of these symptoms is generally subacute in patients with ventriculo-encephalitis, developing over several weeks.[9] In patients with the micronodular form, there may be a syndrome of dementia.[4]

Clinical signs and symptoms alone are relatively insensitive for diagnosis of CMV encephalitis. This neurological complication is difficult to distinguish clinically from AIDS-dementia complex, which is the most commonly observed neurological condition caused by HIV infection. However, confusion, disorientation, apathy and withdrawal are more common among patients with CMV-related encephalitis. Comparatively, symptoms of depression or mental slowing are frequently evident in patients with AIDS-dementia complex (Table 2). Owing to the difficulties of diagnosing, based on signs and symptoms alone, other diagnostic methods are required.

Table 1: Number of cases in an autopsy series (*n*=152) diagnosed with a manifestation of CMV disease either when alive and/or at post-mortem[21]

CMV disease manifestation	Diagnosed alive	Diagnosed alive and/or at post-mortem
Retinitis	17	34
Adrenalitis	0	43
Pneumonitis	2	34
Encephalitis	0	24
Gastrointestinal	5	16
Miscellaneous	1	9
Any manifestation	21	73

CMV, cytomegalovirus.
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CSF examination: Examination of CSF is non-specific for the diagnosis of CMV encephalitis as the CSF profile is variable. CSF analysis in some cases reveals pleocytosis with elevated protein levels and hypoglycorrhachia (CSF glucose level of <40 mg/dl); however, the latter is uncommon.[25]

Cell culture: Culture of the CSF for CMV is a very insensitive, although specific, diagnostic test.[16,20,26,27] It is rarely successful in patients with CMV encephalitis, probably due to the low quantity of virus particles present in this biological fluid. Overall, CSF is culture positive in 10–25% of cases, being more likely when pleocytosis is present.[24] Thus, false negatives may be seen in patients who have suggestive clinical, neuroradiological and histopathological evidence of CMV infection of the nervous system.

Brain biopsy: Brain biopsy is not a useful test in patients with CMV encephalitis as focal lesions are rarely visible on neuroradiological examination. The examination of CNS tissue is limited to autopsy specimens in which histopathology and immunohistochemistry can provide a retrospective diagnosis.

Neuroimaging: Computed tomography (CT) and MRI scans of the brain of a patient with CMV encephalitis may show increased signal intensity in the ependymal surfaces of the ventricles, which is characteristic of periventricular inflammation.[23,28] Using CT, the lesions in the brain parenchyma may appear diffuse, ill-defined and of low attenuation. With MRI, high signal intensity is observed with T_2-weighted images. Atrophy and/or ventricular enlargement are present in 40% of cases. Imaging signs suggestive, or diagnostic, of ventriculitis are seen in approximately 45% and 30% of cases, respectively.[13] While MRI is more sensitive than CT at detecting CMV encephalitis in individuals, both lack sensitivity as they can show normal or non-specific abnormalities in patients with advanced CMV encephalitis.[29]

PCR:

- Diagnosis of CMV infection of the CNS should be performed using PCR detection of viral DNA in the CSF (category 1 recommendation)

The introduction of CSF PCR has allowed better characterization and improved diagnosis of clinical syndromes associated with CMV infection of the CNS.[30] The diagnostic potential of CSF PCR has been evaluated by comparing its data with histopathological observations at autopsy, virus isolation from the CSF and clinical findings.[26,31,32] The sensitivity and specificity of CSF PCR in these studies were more than 80% and 90%, respectively.[26,31–35] Positive and negative predictive values are in the range 86–92% and 95–98%, respectively.[26,32]

CMV viraemia detected by PCR may predict the development of retinitis. CMV detection by relationship between retinitis and the development of CMV neurological disorders suggests that PCR of blood is likely to be of benefit in the management of

Table 2: Clinical features and manifestations of CMV-related encephalitis and polyradiculomyelitis and AIDS-dementia complex [adapted from Delia S, *Herpes*, 1997][15]

Neurological disorder	Clinical features	CSF findings
CMV encephalitis	Acute or subacute confusion	Hypoglycorrhachia*
	Disorientation	Mononuclear pleocytosis
	Memory loss	
	Cranial nerve palsies	
	Fever	
CMV polyradiculomyelitis	Sacral pain paraesthesias	Hypoglycorrhachia
	Sphincter dysfunction	Polymorphonuclear pleocytosis
	Subacute onset of ascending flaccid paraparesis	
AIDS-dementia complex	Forgetfulness	Normal
	Mental slowing	Mild pleocytosis
	Depression	
	Psychomotor slowing	

* Defined as CSF glucose level of <40 mg/dl.
CSF, cerebrospinal fluid; CMV, cytomegalovirus.

encephalitis.[33–35] In prospective studies, samples were obtained from patients who were then followed up and the occurrence of CMV disease was documented. These tests were found to have good sensitivity and specificity (Table 3).[33–35] Thus, PCR of the blood or plasma can be used to predict the development of CMV disease. However, the drawbacks in interpreting these assays are that no consistent method was used, variability is undefined and threshold values are not universally established.

Cytomegalovirus is rarely detected by PCR in the CSF of patients without CMV neurological complications. For example, in a prospective evaluation of nested PCR in CSF, 24 individuals with AIDS and suspected CMV-associated neurological disease had detectable CMV DNA compared with only eight (11%) with other diagnoses.[36] Therefore, PCR is of benefit in confirming CMV-related neurological involvement in patients with AIDS.

Quantification of virus load using PCR: Quantification of virus load in the blood is of greater importance in the diagnosis of CMV infection than its location in tissue. In addition, this method may be used either for diagnosis of CMV-related disease or for follow up during antiviral therapy.[37] Quantitative and semi-quantitative PCR assays and a branched chain DNA assay have been evaluated in patients with CMV-related neurological complications.[37–40]

The CSF of patients with CMV encephalitis may contain up to 10^7 copies/ml of CMV DNA as determined using quantitative PCR. A correlation has been shown between the amount of CMV DNA in the CSF and both the pattern and extent of lesions in the brain. Additionally, more extensive forms of ventriculoencephalitis are associated with a higher CMV DNA CSF load.[37–39]

The CMV virus load may vary because of antiviral drug treatment. A decrease or a clearance of CMV DNA from the CSF has been observed in patients with CMV encephalitis receiving ganciclovir, foscarnet or a combination of the two.[37,38–40]

Association between CMV retinitis and CMV encephalitis: CMV retinitis appears highly correlated to the development of encephalitis in individuals with AIDS (Table 4).[41] Consecutive analyses of 47 post-mortem brain specimens using immunocytochemistry found that 10 of 24 (42%) patients with CMV retinitis had encephalitis. For cases where retinitis was inclusive of the peripapillary region, the association was even stronger, with 75% having encephalitis. The relative risk for the development of CMV encephalitis where CMV retinitis was present was 9.5, increasing to 13 when retinitis involved the peripapillary region.[41]

In a case series of 248 patients who progressed to AIDS in the period January 1983 to December 1995, 14 of 20 patients with CMV encephalitis had concomitant CMV retinitis.[21] While this association is similar to that reported above, the incidence of retinitis was considered to be under-reported as histopathological examination of the eyes of all patients was not performed.

CMV POLYRADICULOPATHY

A commonly observed neurological syndrome is CMV polyradiculopathy, which is often associated with concurrent CMV infection elsewhere in the body.[42] Patients typically develop weakness in the lower extremities. Sacral paraesthesias and acute urinary retention often occur early in the course of the disease. Following this, the syndrome progresses rapidly with the development of a flaccid paralysis beginning in the lumbosacral myotomes and spreading rostrally. Pathological studies have shown CMV infiltration of lumbar and sacral nerve roots.

Diagnosis: MRI can exclude other possible causes of dysfunction of the lower limbs, such as compression of the myelon or *cauda equina* by inflammatory or malignant tumours. Examination of the CSF can reveal hypoglycorrhachia, elevation of protein and pleocytosis (average of 699 cells/mm^3). CSF PCR for CMV can be a useful diagnostic test.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is a clinical entity characterized by rapidly evolving symmetrical limb weakness, loss of tendon reflexes, the absence of or mild sensory signs and autonomic dysfunction. It has been associated with a number of infectious agents including EBV, CMV, and human herpesvirus type 6 (HHV-6) .

Cytomegalovirus has been detected in the sera of between 10% and 15% of cases of Guillain-Barré syndrome.[43–46] One case-control study indicated that patients with demyelinating Guillain-Barré syndrome who have had a recent CMV infection show severe sensory deficits and have anti-GM2 IgM antibody,[47] although this remains to be confirmed by other investigators.[48] However, patients with CMV-related Guillain-Barré syndrome differ from those with *Campylobacter jejuni*-related Guillain-Barré syndrome or those without evidence of either of these infections as they:

- Are significantly younger;
- Have a more severe initial course of the disease;
- Often develop cranial nerve involvement and severe sensory loss (Table 5).[49]

Therapeutic Use of Antiviral Drugs

- CMV disease is always preceded by viraemia (although not always detectable unless frequent

Table 3: Natural history of CMV disease in patients with AIDS defined by different PCR assays[33–35]

Study	CMV disease	PCR results: Positive	PCR results: Negative	Total	Sensitivity	Specificity
Shinkai *et al.*[33]	Yes	24	2	26		
	No	17	51	68		
	Total	41	53	94	92%	75%
Dodt *et al.*[34]	Yes	36	2	38		
	No	27	135	162		
	Total	63	137	200	95%	83%
Bowen *et al.*[35]	Yes	19	0	19		
	No	11	67	78		
	Total	30	67	97	100%	69%

CMV, cytomegalovirus; PCR, polymerase chain reaction.

Table 4. Association between CMV retinitis, peripapillary retinitis and CMV encephalitis in a consecutive analysis of post-mortem brain specimens from patients with AIDS[41]

	CMV encephalitis		
	Present	Absent	Total
Retinitis:			
Present	10	14	24
Absent	1	22	23
Total	11	36	47
Peripapillary retinitis:			
Present	9	3	12
Absent	1	11	12
Total	10	14	24

CMV, cytomegalovirus. Reprinted with permission from *Arch Ophthalmol* 1995;**113:**89–95. © American Medical Association. All rights reserved.

samples are collected). Therefore, therapy should be directed toward the prevention of CMV disease (category 1 recommendation)

- Response to the treatment of established CMV disease (especially CNS disease) remains suboptimal. Every effort should, therefore, be made to prevent the array of CMV diseases by employing treatment strategies shown to be successful in immunocompromised allograft recipients (category 3 recommendation)
- Randomized, controlled trials are needed to define the therapeutic index (efficacy/safety) when existing or new drugs are used for prophylaxis or pre-emptive therapy of CMV CNS disease (research need recommendation)
- Even though patients with CMV-related CNS disease are few in number, better designed, randomized, controlled trials of treatment and management are required (research need recommendation).

The majority of clinical trials investigating the use of oral aciclovir, ganciclovir or valaciclovir were conducted in the pre-HAART era. All studies were well-designed, randomized and double-blind with clinical endpoints usually recording benefits in the prevalence of CMV disease or survival outcomes. However, there have been no prospective, randomized, placebo-controlled clinical trials of therapy for CMV neurological disease, mainly because its incidence is low. Although antiviral therapy appears to prevent or stabilize CMV disease in patients with AIDS, it cannot be assumed that therapy is effective in the prevention of CMV encephalitis.[50] For example, many patients receiving treatment with ganciclovir for other manifestations of CMV disease develop CMV encephalitis.[37,51] Additionally, there is no consistent evidence to suggest that treatment with either drug prolongs survival in this group of patients once CMV is established.[40] Thus, even though in the HAART-era patients with CMV-related disease are few, randomized, controlled trials of antiviral therapy for the prophylaxis or treatment of CMV-related CNS disease are still required. Such trials could employ the treatment strategies shown to be successful in immunocompromised allograft recipients.

Those clinical trials that have prospectively investigated the therapeutic use of aciclovir, ganciclovir or valaciclovir as prophylactic treatment for CMV disease are presented in Table 6.[52–55]

ACICLOVIR

In a randomized, placebo-controlled trial of aciclovir (800 mg four times daily for up to 1 year) in combination with zidovudine versus zidovudine alone in patients with AIDS and advanced AIDS-related complex, the incidence of CMV end-organ disease was too low for any conclusions to be drawn regarding the efficacy of aciclovir for CMV-related neurological disease.[52]

A second, double-blind, placebo-controlled trial randomized patients with advanced HIV infection to receive either high-dose aciclovir (800 mg four times daily) or placebo for up to 1 year.[53] The incidence of CMV disease, the primary end-point, was not reduced with aciclovir therapy; the probability of developing the disease at 1 year was 0.24 and 0.23 in the placebo and aciclovir groups, respectively. However, survival at 1 year, the secondary end-point, was significantly improved in patients treated with aciclovir and the probability of dying was reduced from 0.39 to 0.23; P=0.018.[53] In the trial, four patients receiving aciclovir, but none on placebo, had

Table 5: Clinical characteristics of *C. jejuni*- and CMV-related Guillain-Barré syndrome[49]

	C. jejuni-related Guillain-Barré syndrome	CMV-related Guillain-Barré syndrome
Sex	Predominantly male	Predominantly female
Age	Not specific	Younger
Antecedent episode	Diarrhoea	Upper respiratory infections
Cranial nerve involvement	Less frequent	Frequent facial palsy
Sensory impairment	Less common	Frequent and severe
Electrodiagnosis	AMAN	AIDP
Autoantibody	IgG antibodies to GM1, GM1b, GD1a or GalNAc-GD1a	IgM antibody to GM2

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CMV, cytomegalovirus. Reprinted with permission from Elsevier (*The Lancet Infectious Diseases*, 2001;**1:**29–37).

CMV neurological disease, which was undefined; thus, it is not possible to determine the effect of aciclovir on this manifestation of CMV disease.

GANCICLOVIR

- Ganciclovir is recommended for the therapy of CMV disease; maintenance therapy with ganciclovir can be discontinued if the CD4 count remains above 100 cells/mm^3 for 6 months (category 1 recommendation)

Prophylactic treatment with oral ganciclovir (1000 mg three times daily) reduces the risk of CMV disease in patients with advanced AIDS.[54] In a clinical trial, CMV events were reduced by 49% in patients who received ganciclovir (P<0.001) and occurred irrespective of concomitant use of antiretroviral drugs.[54] In the trial, the most common manifestation of CMV disease was CMV retinitis and no cases of CMV CNS disease were reported. Prophylaxis with ganciclovir was not associated with improved survival but survival free of CMV disease was significantly prolonged. Thus, oral ganciclovir appears to be useful in the prophylaxis of CMV disease but its low bioavailability restricts its use to prophylaxis and maintenance treatment.[56]

VALGANCICLOVIR

- Valganciclovir may be preferred to intravenous or oral ganciclovir under certain circumstances for the treatment of CMV encephalitis. The choice of agent will depend upon the level of function of the patient, their ability to take orally administered drugs and the severity of the disease (category 2 recommendation)
- The potential of long-term valganciclovir therapy to improve mortality and morbidity outcomes in immunocompromised children (e.g. those with HIV or transplant recipients) with CMV CNS disease needs to be assessed (research need recommendation)

Valganciclovir, an orally administered prodrug that is rapidly hydrolysed to ganciclovir, is effective for the long-term management of CMV retinitis in patients with AIDS.[57] A randomized, non-blind study indicated that oral valganciclovir (900 mg twice daily for 3 weeks then 900 mg once daily) and intravenous ganciclovir (5 mg/kg twice daily for 3 weeks then 5 mg/kg once daily) were equally effective in the treatment of newly diagnosed CMV retinitis in patients with AIDS. The progression of CMV retinitis was determined within 4 weeks after the initiation of treatment in 160 individuals with AIDS. Of the patients who could be evaluated, seven of 70 assigned to intravenous ganciclovir (10%) and seven of 71 assigned to oral valganciclovir (9.9%) had progression of CMV retinitis during the first 4 weeks. The median times to progression of retinitis were 125 days in the group assigned to intravenous ganciclovir and 160 days in the oral valganciclovir group. The frequency and severity of adverse events were similar in the two treatment groups. During maintenance therapy with valganciclovir, the most commonly reported adverse events included neutropenia, anaemia, thrombocytopenia, gastrointestinal disease (including diarrhoea, nausea, vomiting and abdominal pain), fever, headache, insomnia, peripheral neuropathy, paraesthesia and retinal detachment.

Studies of long-term valganciclovir therapy in immunocompromised children with CMV CNS disease are warranted to assess the potential for improving morbidity and mortality outcomes.

VALACICLOVIR

Treatment with valaciclovir (8000 mg/day) significantly reduced the incidence of CMV disease by 33% in patients with advanced HIV disease compared with those who received oral aciclovir 3200 or 800 mg/day (P=0.03);[55] the confirmed CMV disease rate was 11.7% among valaciclovir recipients and 17.5% in the pooled aciclovir arm. The time to confirmed CMV disease was significantly longer for the valaciclovir group (P=0.03). Of the cases of CMV disease, CMV retinitis accounted for 79.3% and gastrointestinal disease for 15.2%; the other diagnoses were relatively infrequent. Despite the low numbers of cases of CNS disease, there was a reduction in the number with valaciclovir (1 [0.2%] in valaciclovir recipients; 7 [1%] in the pooled aciclovir groups). However, the dose used was relatively large and there was a higher incidence of a thrombotic microangiopathy (TMA)-like syndrome in the valaciclovir recipients than in the aciclovir recipients (14/523 versus 4/704; P=0.008). A TMA-like syndrome in HIV patients is associated with the use of some antifungal and antibacterial agents,[58] and there is a proposed link with renal insufficiency. The risk of TMA was also increased in HIV patients with CMV disease in one study[59] but not in another.[58] While the cause of a TMA-like syndrome is uncertain, individuals with AIDS have an increased risk

Table 6: Randomized, double-blind clinical trials of antiviral prophylaxis with aciclovir, ganciclovir or valaciclovir in people with AIDS[52–55]

Study (design)	Patients (*n*)	Treatment regimen	CMV disease *n* (%)	Relative risk
Cooper *et al.*[52] pc, mc	129	Aciclovir 800 mg four times daily for up to 1 year	5 (4)	
	136	Placebo for up to 1 year	8 (6)	
Youle *et al.*[53] pc, mc	153	Aciclovir 800 mg four times daily for up to 1 year	4 (3)	
	149	Placebo for up to 1 year	0 (0)	
Spector *et al.*[54] pc, mc	486	Oral ganciclovir 1000 mg three times daily[a] for 1 year	68 (14)	0.51*
	239	Placebo for 1 year	62 (26)	1.00
Feinberg *et al.*[55] mc	523[b]	Valaciclovir 2000 mg four times daily	61 (12)	0.71*
	704	Oral aciclovir either 400 mg twice daily or 800 mg four times daily	123 (18)	1.00

[a]Patients could also receive oral aciclovir up to 1000 mg/day for the treatment of HSV; [b]All patients were seropositive for CMV and had CD4 cell counts <100/mm^3; *P<0.05 vs comparator; mc, multicentre; pc, placebo-controlled; HSV, herpes simplex virus; CMV, cytomegalovirus.

of developing it, and therapy with valaciclovir may increase that risk. Consequently, patients with AIDS who are treated with valaciclovir 8000 mg/day should be monitored for signs and symptoms of TMA. Valaciclovir is not currently recommended for the treatment or prevention of CMV disease.

COMBINATION THERAPY WITH GANCICLOVIR AND FOSCARNET

- Although there is a lack of data from randomized clinical trials, currently available data point to a clear lack of benefit from either ganciclovir or foscarnet therapy of CMV CNS disease (category 3 recommendation)

Case reports have documented ganciclovir and foscarnet concentrations in CSF exceeding the ED_{50}.[60] In an open pilot, non-comparative, multicentre study conducted in the pre-HAART era, combination therapy with foscarnet and ganciclovir (foscarnet 90 mg/kg and ganciclovir 5 mg/kg twice daily for 3 weeks, then foscarnet and ganciclovir at the same doses once daily) improved or stabilized the condition of 74% of 31 HIV-infected patients with either acute CMV encephalitis or CMV myelitis (see Figure 1).[61]

Eight patients did not respond to treatment and 10 withdrew because of adverse effects. Of those who also received maintenance therapy, CMV disease progression was observed in a further 10 patients after a median of 126 days. Overall, median survival was 3 months.[61]

As the response to the treatment of established CMV disease (especially CNS disease) in HIV-infected individuals remains suboptimal, every effort should be made to prevent CMV disease by employing the treatment strategies shown to be successful in immunocompromised allograft recipients. In this setting, the agents are used prophylactically or are initiated when a surrogate marker reaches a threshold (pre-emptive therapy) and such strategies could be applied to the management of individuals with HIV infection. Thus, randomized, controlled trials are needed to show the balance of efficacy/safety when each of these existing or new drugs is used for prophylaxis or pre-emptive therapy.

CMV POLYRADICULOPATHY AND GUILLAIN-BARRÉ SYNDROME

Ganciclovir and foscarnet appear to have some benefit in the treatment of CMV-associated Guillain-Barré syndrome and polyradiculomyelopathy.[13,62,63] A retrospective analysis of patients with AIDS-related CMV polyradiculopathy who received antiviral treatment with ganciclovir and/or foscarnet showed a reduction in mortality from 100% to 22%.[64] Treatment failure in some patients with ascending paralysis may have been caused by drug resistance. Risk factors for treatment failure were prior monotherapy for other CMV-related diseases or persistent CSF pleocytosis in serial CSF analysis.[64]

Therapeutic Use of HAART

- HAART results in reduced risk of CMV disease and prolonged survival following CMV disease in patients with HIV/AIDS (category 1 recommendation)
- Ganciclovir is recommended for the therapy of CMV disease; maintenance therapy with ganciclovir can be discontinued if the CD4 count remains above 100 cells/mm^3 for 6 months (category 1 recommendation)

Highly active antiretroviral therapy has had a profound impact on the natural history of HIV infection. In addition to suppressing plasma HIV load and increasing CD4+ lymphocyte counts, use of the newer therapies has been associated with decreased hospitalizations, incidence of associated opportunistic infections and increased survival.[65] While the short-term clinical

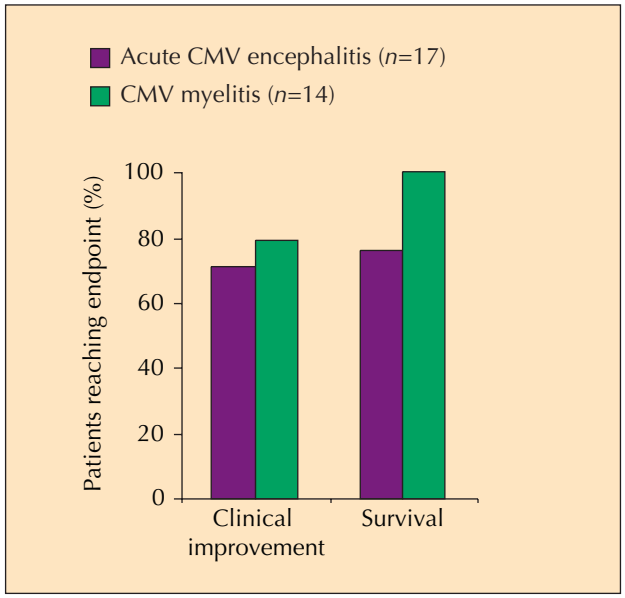

Figure 1:
Patients with HIV infection and either cytomegalovirus (CMV) encephalitis or myelitis who received combination induction therapy with foscarnet 90 mg/kg and ganciclovir 5 mg/kg twice daily for 3 weeks.[61]

impact of potent antiretroviral therapies on HIV infection and the incidence of established opportunistic diseases, including CMV diseases, are clear, the long-term impact is not yet fully defined.[65] Once a patient is established on HAART, CMV maintenance therapy can be discontinued, although the long-term prognosis in patients who have discontinued CMV prophylaxis is unclear.[19] Cohort studies indicate that maintenance can be stopped for patients when CD4+ count remains above 100 cell/mm^3 for more than 6 months (Table 7).[66–74]

In the context of HAART, although antiviral agents are moderately effective in reducing the incidence of CMV disease, they are infrequently used. However, these agents may still be of benefit in patients in whom AIDS is progressing despite HAART, which may be due to poor compliance or failure of therapy.

CMV Resistance to Ganciclovir

- Foscarnet should be reserved for treatment of ganciclovir-resistant CMV because of its toxicity and intravenous mode of administration (category 2 recommendation)
- Ganciclovir-resistant CMV is more common than has been appreciated in the past and the possibility of resistant CMV should be considered in cases of CMV encephalitis (category 3 recommendation)
- Patients not responding to ganciclovir therapy should be evaluated for the emergence of resistance using genotypic analyses (category 3 recommendation)

Many patients receive treatment for CMV prior to the diagnosis of CMV-related neurological disease and may harbour drug-resistant virus.[50,75,76] The potential for resistance has been evaluated in a cohort of 45 patients with AIDS presenting with first-episode retinitis and receiving a median of 7 months of maintenance therapy with ganciclovir.[77] CMV virus load and genetic changes in the UL97 marker for ganciclovir resistance were measured in PCR-positive samples. Of 14 patients who were PCR-positive during treatment, 10 of those (71%) showed evidence of resistance to ganciclovir. None of these patients became PCR-negative for CMV after reinduction with ganciclovir therapy compared with three of four patients without evidence of ganciclovir resistance (P=0.022).[77]

The occurrence of resistant virus can be explained by the replication dynamics of CMV and fitness differences between wild-type and resistant virus. CMV has generally been described as a slow-replicating virus because of the time to appearance of its *in vitro* cytopathic effect.[78] However, it is now known to be a rapidly replicating virus with a doubling time of approximately 1 day *in vivo*.[79] This half-life of CMV is of the same order as that of HIV-infected lymphocytes ($t_{1/2}$=2 days).[80]

Modelling predicts that short-term ganciclovir therapy (i.e. less than 3 weeks) will not result in a substantial increase in the proportion of ganciclovir-resistant CMV strains, even though the resistant virus is fitter (5–6%) than the wild type (Figure 2).[81] For example, even if the resistant virus made up 0.5% of the initial population, given its relative fitness, it would still represent less than 2% of the population at 21 days. Moreover, in the absence of selective pressure (i.e. upon cessation of therapy), the resistant virus does not persist and returns to baseline levels after 42 days. In contrast, during long-term ganciclovir therapy, the resistant virus will continue to replicate at the expense of the wild-type virus, with the result that by Day 145 it accounts for 30% of the population, and by Day 150 for more than 90% of the total virus.

In summary, ganciclovir resistance appears to be a cause of treatment failure and occurs at higher frequencies than generally appreciated.[77,82,83] Therefore, patients not responding to therapy should be evaluated for ganciclovir-resistant CMV using genotypic analyses.

As the majority of ganciclovir-resistant CMV isolates are UL97 mutants, they remain susceptible to foscarnet. Thus, foscarnet (180 mg/kg per day as intermittent infusion) may be a suitable antiviral treatment in ganciclovir-resistant patients. In patients with documented multiple antiviral drug resistance, ganciclovir in combination with foscarnet may be an option. However, the efficacies of foscarnet or the combination of foscarnet and ganciclovir have not been established at this time.

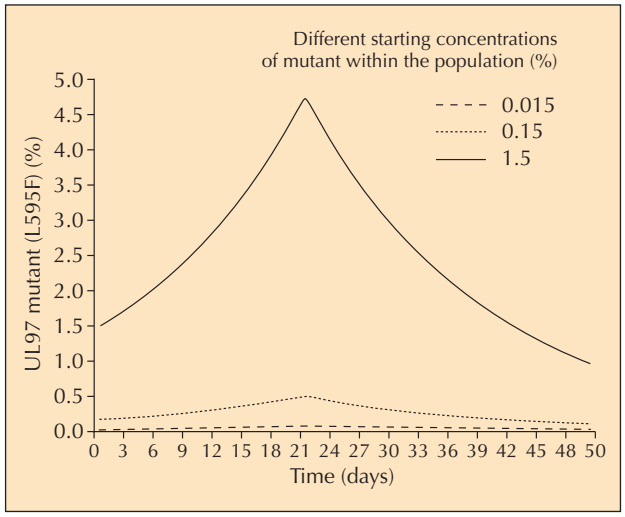

Figure 2:
Model of the proportion of UL97 mutants within the population after the initiation of ganciclovir therapy.[81] *Reproduced with permission from Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy.* Proc Natl Acad Sci USA *2000;***97:***8039–8044. © 2000 National Academy of Sciences USA.*

Conclusions

Cytomegalovirus infection has been associated with the development of CMV encephalitis, various peripheral nerve syndromes and Guillain-Barré syndrome. Reactivation of CMV is the most common opportunistic viral infection in patients with HIV and is responsible for a significant proportion of morbidity and mortality in patients with AIDS. CMV retinitis is highly correlated with the development of encephalitis in patients with AIDS, especially when it involves the peripapillary region. Clear associations between neurological disorders and CMV infection in patients with HIV are difficult to define *in vivo*, as co-infection with other viruses is the norm.

Polymerase chain reaction of CSF is of benefit in confirming CMV-related neurological disease in patients with AIDS, and diagnosis of active CMV infection should be made using this technique.

A decrease or clearance of CMV DNA from the CSF has been observed in patients with CMV encephalitis receiving ganciclovir, foscarnet or a combination of the two drugs. Ganciclovir and foscarnet, administered either alone or in combination, stabilize the condition of patients with CMV disease, but do not have appreciable effects on survival.

Highly active antiretroviral therapy is effective in reconstituting the immune system such that CMV infection can be controlled in patients with HIV/AIDS. As such, it has led to a dramatic decrease in AIDS-related mortality. Ganciclovir and foscarnet may still be of

Table 7: Studies where CMV maintenance therapy for CMV retinitis was discontinued after HAART[66–74]

Study	*n*	CD4+ count (cells/mm^3)	HIV load (copies/ml)	CMV viraemia	Time from CMV retinitis (months)	Duration of HAART (months)	Follow-up (months)	Number with relapse
Tural *et al.*[66]	7	230	<200	PCR-negative	11	3	9	0
Vrabec *et al.*[67]	8	255	<500	NT	NR	7.9	11.4	0
Macdonald *et al.*[68]	11	183	8912	NT	18	9	5.2	0
Jabs *et al.*[69]	15	297	<2343	NT	21	17	8	0
Kirk *et al.*[70]	5	179	29	NT	NR	18	12	0
Di Perri *et al.*[71]	8	105	<500	pp65 <20 cells/ 10^6 WBC	NR	3.1	22.5	0
Whitcup *et al.*[72]	14	317	NR	Transient	22.8	NR	16.4	0
Mezzaroma *et al.*[73]	5	>200	NR	NT	NR	12	12	0
Soriano *et al.*[74]	5	>100	<500	NT	NR	3	8	0

NR, not reported; NT, not tested; WBC, white blood cell; CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; PCR, polymerase chain reaction.

therapeutic benefit in patients in whom AIDS is progressing despite HAART. While the short-term clinical impact of HAART on HIV infection and the incidence of established opportunistic diseases are clear, the long-term impact remains to be established. Maintenance therapy with ganciclovir can be stopped once HAART treatment is established, although the long-term prognosis in patients who have discontinued CMV prophylaxis is unclear.

As the response to the treatment of established CMV disease (especially CNS disease) in HIV-infected individuals remains suboptimal, randomized, controlled trials are required to show whether strategies shown to be successful in immunocompromised allograft recipients, such as prophylactic and pre-emptive regimens, are beneficial.

Address for correspondence:
Professor P Griffiths, Department of Virology, Royal Free and University College Medical School of UCL, Hampstead Site, Rowland Hill Street, London NW3 2PF, UK

E-mail: pgriffiths@rfc.ucl.ac.uk

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