

Cytomegalovirus Infection in Patients with HIV Infection

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Abstract

Cytomegalovirus (CMV) is responsible for the most common viral opportunistic infection in persons with acquired immunodeficiency virus syndrome (AIDS). Clinical disease due to CMV has been recognized in up to 40% of patients with advanced HIV disease. The most common presentation is retinitis, although colitis, esophagitis, pneumonitis and neurological disorders are also reported frequently.

CMV retinitis is usually diagnosed clinically, and serological testing for CMV immunoglobulin is useful to support the diagnosis. Parts of the gastrointestinal tract (esophagus and colon) are the most common extraocular sites of CMV infection in AIDS patients.

Therapy with systemic agents, including intravenous ganciclovir, intravenous foscarnet, and intravenous cidofovir, is effective. Ganciclovir is associated mainly with hematological toxicity, while foscarnet and cidofovir are nephrotoxic. Intravitreal injections with these antiviral agents are also effective, but inconvenient, and there is a need for repeated injections. Intraocular implants that slowly release ganciclovir have been effective for both acute therapy and long-term maintenance, but the occurrence of contralateral ocular and extraocular disease is a serious concern. New agents, as for example an anti-sense agent against CMV, appear promising.

Key Words: Cytomegalovirus infection, human immunodeficiency virus, CMV retinitis, CMV colitis, AIDS.

Epidemiology

Cytomegalovirus (CMV) causes the most common viral opportunistic infection in persons with acquired immunodeficiency syndrome (AIDS). Clinical disease due to CMV has been recognized in up to 40% of patients with advanced HIV disease (1–3). The most common presentation is retinitis, although colitis, esophagitis, pneumonitis and neurological disorders are also reported frequently.

CMV is a double-stranded DNA virus in the herpesvirus family. In HIV-infected persons, as with most herpes infections and other opportunistic infections associated with HIV infection, CMV disease is due to reactivation of the latent virus in a previously infected host. Seroprevalence of CMV ranges from 30–100%, depending on the population surveyed. The presence of CMV antibody in the male homosexual population is higher than in the male heterosexual population and more common with persons of lower socioeconomic status (4, 5). Almost 100% of homosexual men with HIV infection have serologic evidence of either recently acquired or reactivated CMV infection (1).

Despite the high prevalence of CMV antibody in HIV infection, the clinical manifestations of CMV disease do not generally present until the CD4 count drops below 100 CD4 cells/mm³ (3, 6). In a study of 31 persons with HIV-infection and CMV retinitis, the mean CD4 count was 29 cells/mm³ and the median was 17 cells/mm³ (7). A multicenter observational cohort study of 1002 HIV-infected persons with fewer than 250 CD4 cells/mm³ who were receiving zidovudine showed that disease due to CMV developed in 109 persons (8). Kaplan-Meier estimates of the proportion of persons who developed CMV disease were 21.4% at 2 years for persons entering the study with fewer than 100 CD4 cells, and 10.3% for persons with initial counts greater than 100 cells/mm³. Of the 109 persons developing CMV disease, 93 (85.3%) were diagnosed with retinitis, 10 (9.2%) with esophagitis, 3 (2.7%) with both retinitis and esophagitis, 8 (7.3%) with colitis, and 1 each with gastritis, hepatitis, and encephalitis.

CMV Retinitis

CMV retinitis is the most common ocular infection in AIDS and is an important cause of morbidity. With better treatment of the primary HIV infection, prophylaxis against *Pneumocystis carinii* pneumonia, and a resultant longer survival, the prevalence of CMV retinitis appears to be increasing (9).

Patients may present with symptoms of blurred vision, a scotoma or dark area covering part of the visual field, light flashes, or floaters. However, a significant percentage of infected patients are often asymptomatic despite the presence of extensive or vision-threatening CMV retinitis. In one study, fewer than 50% of AIDS patients with CMV retinitis had visual symptoms (10). Other studies have estimated that about 5% of visually asymptomatic AIDS patients have CMV retinitis (11, 12). Therefore, periodic ophthalmologic examination utilizing indirect ophthalmoscopy should be performed in those patients with CD4+ lymphocyte counts below 100/mm³. In addition, one study utilizing formal perimetry detected visual field defects in 70% of patients with CMV retinitis

(13). This suggests that patients should check their own vision in each eye separately on a daily basis and report to their physicians at once any alterations in their field of vision. A self-screening chart designed for this purpose was found in one study to detect scotomas in 63% of patients with previously undiagnosed CMV retinitis (14).

Due to the difficulty and associated morbidity of obtaining retinal tissue for histopathological examination, the diagnosis of CMV retinitis is usually based on its distinct clinical appearance of retinal necrosis. This most commonly manifests as a whitish opacification of the retina with exudates and variable amounts of hemorrhage (15). The appearance of this lesion may vary depending upon the location and rate of disease progression. A granular appearance is more typical of lesions which begin in the peripheral retina or of more slowly progressive lesions. These lesions are more likely to give rise to symptoms of light flashes or floaters. Lesions initially involving or adjacent to the optic nerve and macula (sight-threatening lesions), as well as more rapidly progressive disease, tend to have a more fluffy and edematous appearance. These lesions are more likely to cause visual field defects or blurred vision. Associated edema or subretinal fluid involving the macula can cause blurred vision which is reversible with anti-CMV treatment. However, any vision loss or visual field defect due to direct involvement by the virus is usually permanent. As the lesions enlarge, they tend to follow the course of the retinal vessels, forming large, wedge-shaped areas of involvement. Where there is a large amount of associated hemorrhage, it may resemble a slice of "pizza with cheese and catsup" (Fig. 1). Patients with AIDS and CMV retinitis typically have minimal ocular inflammation.



Fig. 1. CMV retinitis showing vascular sheathing. Along the vessel arcade, there is also edema and subretinal hemorrhage.

However, recently (16) AIDS patients with CMV retinitis controlled by chronic maintenance therapy and treated with highly active antiretroviral therapy which includes protease inhibitors have been observed to develop uveitis, vitreitis, and macular edema in the involved eye. This is unaccompanied by any visible activity of CMV retinitis and responds variably to topical anti-inflammatory agents or corticosteroids. CMV retinitis did not reactivate in the 2 patients treated with oral or periocular corticosteroids. This may represent an enhanced immune response to CMV.

About half the cases of CMV retinitis are bilateral at presentation (17), and if untreated about 60% of initially unilateral cases become bilateral (18). The presence of positive blood cultures for CMV is neither necessary nor sufficient to make the diagnosis of CMV retinitis. In one study, although all 24 patients had positive urine cultures for CMV at the time of diagnosis of CMV retinitis, only 15 of 24 (63%) had positive blood cultures (6). However, serology to CMV-IgG should be positive in all patients; retinitis in a CMV-seronegative individual is unlikely to be due to CMV.

Other entities may mimic CMV retinitis. Cotton-wool spots are microinfarcts of the retinal nerve fiber layer that occur commonly in persons with HIV infection (19). These lesions do not affect vision and spontaneously regress over several weeks. A near absence of hemorrhage or unusually rapid progression is more typical of progressive outer retinal necrosis (PORN) due to varicella-zoster virus (20). Intraocular lymphomas may present as retinochoroidal infiltrates, optic nerve head swelling and vascular sheathing. *Toxoplasma* chorioretinitis is usually associated with a moderate-to-severe inflammation in the vitreous (21). However, atypical cases with minimal inflammation can occur in AIDS. *Pneumocystis carinii* chorioretinitis appears as discrete multifocal, white-yellow, choroidal lesions with no inflammation (**Fig. 2**) (22).

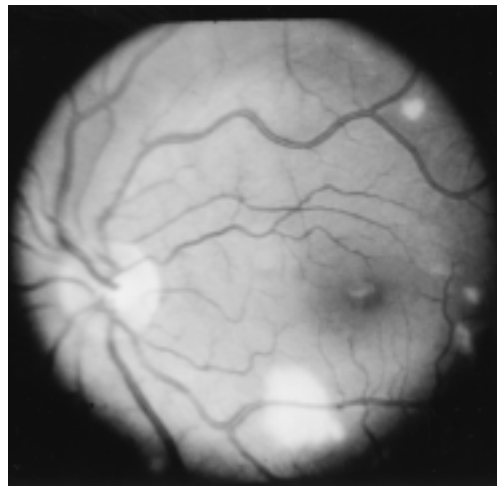


Fig. 2. *Pneumocystis carinii* retinitis.

Despite appropriate antiviral treatment, up to 20–30% of patients with CMV retinitis may develop retinal detachments with a cumulative risk estimated to be 30–50% at one year (23, 24). Retinal detachments are more likely with larger areas of involvement of the peripheral retina and with continued activity of the retinitis (23–25). The detachments can often be anatomically repaired successfully with the use of vitrectomy techniques and the instillation of silicone oil, with retention of functionally useful vision. The long-term visual prognosis, however, is guarded (26–28).

CMV of the Gastrointestinal System

Gastrointestinal involvement with CMV is a significant problem in patients with AIDS. It is the most common extraocular manifestation of CMV infection in AIDS patients.

Involvement of the esophagus with CMV occurs in approximately 10% of persons with AIDS (29). The most common presentation is odynophagia, although the most common cause of odynophagia in persons with AIDS is *Candida* esophagitis.

The diagnosis of CMV esophagitis is made from the histopathological evidence of CMV with an inflammatory response in the appropriate clinical setting. The presence of extensive, large, shallow mucosal ulcers in the distal esophagus is the classical sign of the disease (30). Histopathologically, large intranuclear inclusion bodies can be seen in the epithelial cells at the edge of the ulcer.

Esophagitis may result from infections due to *Candida*, herpes simplex, histoplasmosis, human immunodeficiency virus, *Mycobacterium tuberculosis* and rarely *M. avium-intracellulare* complex, and *Pneumocystis carinii*, as well as reflux or peptic ulcer disease and lymphoma (31). Due to the prevalence of *Candida* esophagitis in this population, one can treat esophageal symptoms empirically, especially in the presence of oral thrush, with ketoconazole or fluconazole, and endoscope only those persons who fail to respond.

CMV colitis can occur in up to 10% of persons with AIDS (8). Diarrhea, abdominal pain, fever, weight loss and anorexia are frequently present. Extensive gastrointestinal hemorrhage and perforation can also occur. The radiographic manifestation of CMV colitis is nonspecific and may mimic the findings of other inflammatory bowel conditions, including ulcerative colitis (31).

Evaluation in this group of patients should also include flexible sigmoidoscopy or colonoscopy with biopsy and culture. One should exclude other gastrointestinal pathogens such as *Cryptosporidium*, *Microsporidian*, *Giardia lamblia*, *Entamoeba histolyticum*, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Mycobacteria*, and *Clostridium difficile*. In addition, lymphoma, Kaposi's sarcoma, and inflammatory bowel disease must be considered.

Although CMV involvement of the liver and biliary tract is often noted only at autopsy, hepatitis proven clinically to be secondary to CMV is rare in persons with HIV infection (1). Biliary tract or hepatic involvement by CMV may present with right upper quadrant pain and elevated

alkaline phosphatase, mimicking infection with *M. avium-intracellulare* complex and *Cryptosporidium*.

Pancreatitis in HIV-infected persons is noted to be increasing in frequency. CMV has been found to be the most common viral agent associated with this condition (28–34). The presentation is similar to other forms of pancreatitis, i.e., abdominal pain, nausea, vomiting, cachexia, abdominal tenderness, and hypoactive bowel sounds. However, some of these patients may have only a mild increase in amylase and a marked increase in lipase (34).

CMV Pneumonitis

CMV is seldom implicated ante mortem as an isolated pathogen causing pneumonitis in persons with HIV infection (35), but CMV is a common cause of interstitial pneumonitis in immunocompromised patients, especially patients with bone marrow transplant. Murray et al. (35) studied a large group of AIDS patients with active symptomatic pneumonitis. Seventeen per cent were found to have CMV by culture. Two-thirds of these, however, had coexistent *Pneumocystis carinii* pneumonia (PCP) and only 4% had CMV as the sole pulmonary pathogen (36). Recently, Jacobson et al. (37) found that the morbidity and mortality of coexisting CMV infection with PCP were comparable to that of PCP and do not adversely affect the prognosis of PCP in AIDS since CMV is frequently isolated from bronchoalveolar fluid and lung tissue.

Clinical presentations of CMV pneumonitis have ranged from asymptomatic viral shedding to rapidly fatal pneumonia. An interstitial pneumonitis with fever, dyspnea, dyspnea on exertion, nonproductive cough, and hypoxemia is most commonly noted. Diagnosis of CMV pneumonitis should only be made by histological identification of multinucleated CMV inclusion bodies in lung tissue, and other pulmonary pathogens, such as *P. carinii*, *M. tuberculosis*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Streptococcus pneumoniae* and *Hemophilus influenzae*, should be excluded.

CMV Neurological Diseases

In autopsy studies, CMV disease in the central nervous system has been found in 25% of persons with HIV infection (38–41). Pathological diagnosis is based on finding typical inclusion bodies, or by immunohistochemical or *in situ* hybridization techniques. Pathologic findings are: necrotizing lesions with microglial nodules, focal parenchymal necrosis, necrotizing ventriculoencephalitis, and radiculomyelitis.

Clinically neurologic syndromes caused by CMV in AIDS are usually unrecognized. Encephalitis (38–40), polyradiculoneuritis (42) and peripheral neuropathy (43) have been reported. A polyradiculoneuritis due to CMV has been recently identified as a progressive polyradiculoneuropathy associated with distinct cerebrospinal fluid abnormalities, including a predominantly polymorphonuclear pleocytosis and hypoglycorrachia (44).

It is noteworthy that a recent autopsy study showed that 42% of patients with CMV retinitis

had CMV encephalitis, with the prevalence of encephalitis increasing to 75% if the retinitis was adjacent to or involved the optic nerve. And 91% of those with CMV encephalitis had CMV retinitis (45). Therefore, an ophthalmologic evaluation is indicated in AIDS patients with CMV encephalitis and may be of diagnostic value in AIDS patients with neurological symptoms.

Diagnosis of CMV Diseases

As mentioned earlier, most CMV diseases are diagnosed by histological biopsy, except retinitis, which is diagnosed by clinical observation in conjunction with serodiagnosis or culture and clinical setting.

The most common method currently used to detect CMV is either by culture or by the more rapid modification of this procedure called the shell-vial method (46). However, these detection methods have limitations. Cultures require fresh samples and may take up to several weeks to provide a reliable answer. The shell-vial method may be faster, usually requiring 48 hours. However, because they are time-consuming procedures and correlate poorly with clinical disease, these assays are not generally used as part of the management of clinical CMV disease.

Newer methods for detection of CMV viremia have been developed, such as polymerase chain reaction (PCR) (47) and detection of antigen pp65 by the antigenemia test in peripheral blood polymorphonuclear leukocytes (48).

Earlier results have shown that both methods are useful in predicting development of CMV disease up to several months prior to clinical disease. Qualitative plasma CMV DNA has a high sensitivity (89%) and good specificity (75%) for predicting development of CMV disease; pp65 antigenemia uses monoclonal antibodies against a lower-matrix phosphoprotein (pp65) of the CMV (48). Measurement is technician-dependent and, therefore, standardization between laboratories may be difficult. Dodt et al. (49) have demonstrated that CMV serology has no predictive value. The PCR test has detected CMV DNA a median of 46 days before the onset of disease. This was earlier than the 34 days median time for the antigenemia test and a median of 1 day for CMV blood cultures. Multivariate analysis showed that the PCR method is superior to other tests (odds ratio: CMV PCR 10.0, antigenemia test 4.4 and CMV cultures 4.3) (49).

Shinkai et al. (50) compared the results of culturing CMV from plasma and urine with that of determining the plasma PCR in 99 patients. They found that the plasma PCR was superior to culture for identification of AIDS patients at risk for CMV disease, and that quantitation of plasma DNA further identifies high-risk persons.

Branched DNA signal amplification for CMV viral load is in development. Earlier results showed that it can quantify CMV very accurately, but lacks sensitivity in the lower range (51).

Treatment

Ganciclovir

Ganciclovir (DHPG) is a nucleoside analog which inhibits herpes virus DNA polymerase. Its action depends on phosphorylation in CMV-infected cells. Most strains of CMV resistant to ganciclovir are unable to phosphorylate ganciclovir. The drug is virustatic against CMV. Thus, when treatment for disease is stopped, viral spread and progression of disease characteristically recur (3).

In uncontrolled trials, treatment with ganciclovir resulted in the improvement or stabilization of CMV retinitis in 80–90% of patients (52). The median time to clinical progression could be as long as 145 days from the diagnosis of CMV retinitis, while continuing some maintenance therapy with ganciclovir.

However, in a randomized, controlled trial comparing ganciclovir with delayed therapy using strictly graded photographic endpoints, progression of retinitis while on ganciclovir occurred in a median of 50.5 days, compared with the progression on delayed therapy, which occurred in a median of 15 days (53). Similarly, the results of the Studies of the Ocular Complications of AIDS (SOCA) demonstrated the median time to progression of CMV retinitis while on ganciclovir was 56 days (54).

Although the efficacy of ganciclovir for CMV gastrointestinal infection in AIDS patients is less well documented, therapeutic trials utilizing dosing regimens similar to that for retinitis showed good clinical responses. However, unlike the situation with CMV retinitis, because the cells lining the gastrointestinal tract regenerate rapidly, therapy can often await development of moderate-to-severe symptoms in order to justify the use of toxic systemic therapy. Likewise, there is no consensus that maintenance therapy is necessary or beneficial, especially since the risk of development of resistant CMV increases with maintenance therapy (55, 56).

The utility of ganciclovir therapy in the treatment of CMV pneumonitis is anecdotal. In bone marrow transplant recipients, the combination of ganciclovir with high-dose-intravenous immunoglobulin has been shown to be more effective. This experience appears not to be the case in persons with AIDS (57).

Neutropenia and thrombocytopenia are the major dose-limiting toxicities of ganciclovir therapy. Because ganciclovir and zidovudine are both myelosuppressive, it is difficult to administer these agents concurrently. However, this problem has been ameliorated by the availability of non-myelosuppressive antiretroviral agents such as didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) and by the use of granulocyte growth factors (e.g., G-CSF and GM-CSF).

Intravitreal injections of ganciclovir have been used for treatment of CMV retinitis in persons unable or unwilling to tolerate systemic therapy with ganciclovir or foscarnet (58, 59). Concentrations greater than the ID_{50} for most strains of CMV can be maintained for 60 hours after

a single 200 µg injection (59). Two injections of 200–400 µg per week are normally given for 2–3 weeks during an induction period, followed by weekly maintenance injections. The dosages appear equally effective without clinically apparent toxicity. This method appears to be about as effective as intravenous therapy. One group has used repeated intravitreal injections of 2 mg of ganciclovir in conjunction with intravenous therapy, with no evidence of toxicity (60). Inadvertent injection of 40 mg did result in severe retinal toxicity (61).

An implantable intraocular device that allows the slow, sustained release of ganciclovir to the vitreous over 6–8 months has been developed (**Fig. 3**). Twenty-six patients (30 eyes) with CMV disease limited to the peripheral retina were randomized to receive immediate treatment with this device, or to observation with deferred implantation of the device when the retinitis progressed (62). The median time to progression was 15 days in the deferred group versus 226 days in the immediate treatment group. Ultimately, 39 eyes received implants. The time to progression was much longer with the intraocular device than that experienced with systemic therapy in the SOCA study. However, the lack of systemic therapy increases the risk of CMV disease in other organs as well as in the second eye by 50% at 6 months.

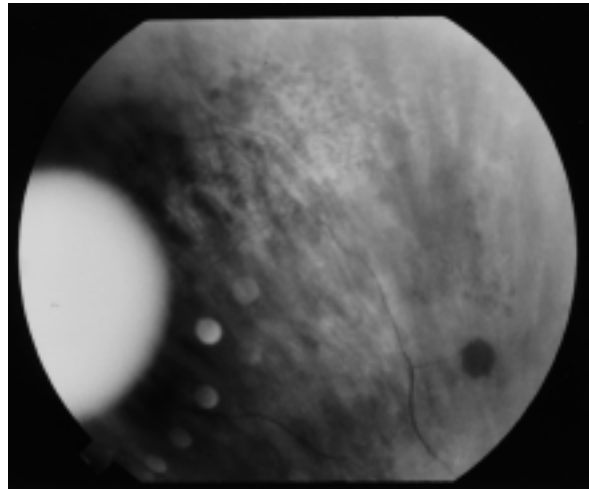


Fig. 3. Ganciclovir implant as observed through the lens. Opposite the implant, there is evidence of healing CMV retinitis.

A larger randomized trial compared an implant delivering 1 µg/hour, an implant delivering 2 µg/hour, and intravenous ganciclovir in AIDS patients with newly diagnosed CMV retinitis (63). The median time to progression with each implant (221 days and 191 days respectively) was significantly longer than with intravenous (IV) ganciclovir (71 days). However, the risk of second eye involvement was only half as great with IV therapy. Similarly, patients receiving IV therapy were less likely to develop extraocular CMV (0% vs 10.3% in the implant groups). Thirty-one percent (31%) of the implanted patients developed biopsy-proven visceral disease, and CMV disease

was present in 3 out of 4 additional patients at autopsy. At least one death was attributed to CMV. In comparison, systemic treatment in the SOCA study resulted in a 3–4% incidence of non-ocular CMV disease (64) and a 16–27% risk of second eye involvement (54). A second operation was performed on the patients who had the intraocular implant to replace the device once it was depleted of the drug. Nine eyes, however, developed progression of retinitis prior to the 32 weeks estimated to be the safe replacement time.

Complications of retinal detachment, intravitreal hemorrhage, endophthalmitis, improper placement and damage to the lens have been reported (11–13, 58). In an effort to address the issues of systemic CMV and contralateral ocular involvement, a randomized controlled study was performed comparing an intravitreal ganciclovir implant (IGI) plus oral ganciclovir (1.5 grams three times daily) with an IGI plus oral placebo, and intravenous ganciclovir (65). The incidence of biopsy-proven CMV disease or CMV retinitis was 22.4%, 37.8%, and 17.9% respectively. Oral ganciclovir statistically significantly reduced the risk of new CMV disease compared to placebo. However, among the subgroup of patients receiving concomitant HIV protease inhibitor therapy, the incidence of new CMV disease was low and not significantly different between treatment groups. Overall, oral ganciclovir also reduced the incidence of new AIDS-associated conditions, particularly Kaposi's sarcoma.

As described above, an oral form of ganciclovir has become available recently. The bioavailability of ganciclovir administered orally with food averaged 9% (66). Daily doses of 3000 mg or more yielded average serum ganciclovir concentration exceeding 0.5 µg/mL (67), a concentration sufficient to inhibit most clinical isolates of CMV *in vitro* (68).

An open-label, randomized study in patients with AIDS and newly-diagnosed, stable CMV retinitis was performed comparing oral with IV ganciclovir (69). On the basis of the masked assessment of photographs from 115 subjects, the mean time to the progression of retinitis was 62 days in those given IV ganciclovir and 57 days in those given oral ganciclovir ($p=0.63$, $RR=1.08$). However, on the basis of fundoscopy by ophthalmologists who were aware of the subjects' treatment assignments, the mean time to progression was 96 days in subjects given IV versus 68 days in subjects given oral ganciclovir ($p=0.03$, $RR=1.68$). Survival and changes in visual acuity were similar in the two groups. The difference in mean time to disease progression was thought likely to be due to the bias of the ophthalmologists, who were more ready to reinduce or to switch therapy in those patients receiving the drug orally. However, it is also possible that the treating ophthalmologists could detect CMV retinitis in the peripheral retina that is unable to be photographed or may detect clinical progression that does not meet the photographic criteria for progression in the study. Furthermore, patients receiving the oral drug were more likely to develop lesions in the initially uninvolved eye than those receiving intravenous ganciclovir. It has also been noted that reactivation is more difficult to identify ("creeping scars") in patients receiving oral ganciclovir (70). Oral ganciclovir may therefore not be appropriate for patients with lesions close to the fovea or the optic disc. In spite of these shortcomings, oral ganciclovir was deemed to be safe and effective as maintenance therapy for CMV retinitis, and is more convenient for patients to take

than is IV ganciclovir. There is recent evidence that a higher oral dosage, up to 2 grams tid, may be more effective for maintenance therapy (71).

Foscarnet

Foscarnet inhibits DNA polymerase and prevents chain elongation by blocking nucleoside binding sites of all herpesvirus. Specifically, it prevents the cleavage of pyrophosphate from adenine triphosphate and does not require phosphorylation for activation (3). In addition to its inhibitory activity against the herpes DNA polymerase (*herpes simplex* 1 and 2, VZV and CMV), foscarnet has activity against the reverse transcriptase of HIV (72, 73).

Like ganciclovir, foscarnet is only virustatic, and lifelong treatment of retinitis with this drug is required. The major toxicities of foscarnet are its effects on renal function and serum electrolytes, especially calcium. Prevention of nephrotoxicity has been minimized by concurrent infusion of IV saline solution. Frequent monitoring of serum creatinine, creatinine clearance, serum electrolytes, calcium and magnesium is required.

The efficacy of foscarnet was demonstrated initially in uncontrolled trials (73–76). Approval of foscarnet was largely based on the results of a randomized, controlled clinical trial conducted at the NIH (6). The results of the SOCA trial showed that foscarnet and ganciclovir are equally efficacious (54). However, patients who received foscarnet had a longer median time of survival. This was speculated to be secondary to the fact that most patients on ganciclovir were unable to take zidovudine and that foscarnet was active against HIV. However, differential zidovudine use could not fully explain these results. Furthermore, both drugs had a significant suppressive effect on circulating p24 antigen, with no statistical difference between the two drugs (77).

With increasing use of ganciclovir for prolonged periods of time, ganciclovir-resistant strains of CMV are becoming more frequently recognized (56). Foscarnet has been used successfully to treat CMV retinitis in patients with ganciclovir-resistant CMV (78). However, foscarnet-resistant CMV retinitis also occurs with prolonged therapy. Viral sensitivity testing may possibly be useful in helping to direct therapy in the future (79).

Intravitreal injections of foscarnet have also been used to treat CMV retinitis at a dosage of 1200 µg. Vitreous levels remain above the mean 50% inhibition value for CMV for about 56 hours (80). An induction regimen of 2 injections weekly for 3 weeks, followed by once-weekly maintenance injections, is recommended (80, 81). Although there is less experience than with intravitreal ganciclovir, the efficacy and toxicity appear to be comparable. A higher dosage of 2400 µg has been used successfully (79).

Clinical efficacy of foscarnet against gastrointestinal infections due to CMV has been reported. In a study involving 14 AIDS patients with CMV gastrointestinal infection who failed ganciclovir, Dieterich et al. (82) showed that substitution with foscarnet was effective in inducing remission.

The combination of ganciclovir and foscarnet has also been used to treat CMV infection in AIDS patients. Preliminary results demonstrated that simultaneous combination therapy for CMV retinitis is better than foscarnet or ganciclovir alone in patients with clinically resistant CMV retinitis (83–86). The CMV Retinitis Retreatment Trial sponsored by SOCA has recently been completed (87). Patients were randomly assigned to standard treatment with ganciclovir or foscarnet, or to combination therapy (ganciclovir, 5 mg/kg daily and foscarnet, 90 mg/kg daily). The results of the study showed that combination therapy produces a longer median remission (4.3 months) than either ganciclovir alone (2.0 months) or foscarnet alone (1.3 months) and less loss of visual field than with either monotherapy. However, the combination therapy did have a greater negative effect on quality-of-life measures.

The recommended maintenance dosage for foscarnet is either 120 mg/kg or 90 mg/kg once daily with adjustments for calculated creatinine clearance. However, there is evidence that the higher dosage is more effective in controlling CMV retinitis (87) and has greater survival benefit (88, 89).

Cidofovir

[(S)-1 (3-hydroxy-2-(phosphonmethoxy)propyl] cytosine (HPMPC) or cidofovir, a nucleotide analog, has been found to be active against CMV. Being a nucleotide, it does not require phosphorylation in CMV-infected cells. The drug is unique because of its prolonged intracellular half-life (17–65 h) and prolonged *in vitro* and *in vivo* antiviral effects in animal models against CMV and herpes virus (90). Oral probenecid given in high doses before, during, and after infusion, as well as concomitant intravenous hydration, is necessary to prevent severe nephrotoxicity. In a controlled randomized study (Gilead study #107), patients received 5 mg/kg IV once a week for 2 weeks and then, by randomization, either 5 mg/kg or 3 mg/kg once every other week. Interim analysis of the first 60 patients found that the median time to retinitis progression was 115 days in the higher dose group and 49 days in the lower dose group. Creatinine elevation occurred in 2 patients in each group. Probenecid caused adverse reactions in 48% of the patients, with severe but reversible reactions in 2 (3%) (91). SOCA compared deferral of therapy in 64 previously untreated patients with small, peripheral retinitis lesions, to intravenous cidofovir 5 mg/kg with further randomization to a maintenance dosage of 3 mg/kg or 5 mg/kg every 2 weeks. The median time to progression in the low-maintenance dose group was 64 days compared to 21 days in the deferred group ($p=0.52$). The median time to progression was not reached in the high-maintenance dose group and was 20 days in the deferral group ($p=0.009$). Two cidofovir recipients developed persistent elevations of serum creatinine of more than 2.0 mg/dL (92).

In a randomized controlled study (Gilead #106) in patients with newly diagnosed CMV retinitis, IV cidofovir 5 mg/kg weekly for 2 weeks followed by maintenance every 2 weeks delayed the median time to progression from 22 to 120 days ($p<0.0001$). Twenty-four percent (24%) developed treatment-limiting nephrotoxicity. Probenecid side effects occurred in 56% but were dose-limiting in only 7% (93). Given better efficacy in the 5 mg/kg group and the fact that toxicity was comparable to that of the 3 mg/kg group, the dose of choice for maintenance treatment is 5

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mg/kg every other week.

It recently has been recognized that iritis may occur in about one-fourth of patients receiving intravenous cidofovir, with a cumulative incidence of 50% after 125 days of therapy (94). Ocular hypotony may also occur as a complication of IV cidofovir (94, 95).

Prevention

Since CMV infection is a major cause of morbidity and mortality in late-stage HIV infection (CD4 < 100), therapeutic strategies to prevent CMV infection in this group become meaningful.

A double-blind, placebo-controlled study reported by Spector et al. (96) showed that oral ganciclovir (1000 mg 3 times daily) was beneficial in patients with CD4 lymphocyte counts less than 100/mm³ (study #1654). At entry into the study and every 2 months thereafter, ophthalmologic examinations were performed and viral cultures were obtained. The rate of dissemination of CMV disease (primarily CMV retinitis) among 725 patients was 39% in placebo recipients compared with 20% in those who received oral ganciclovir (p=0.001). There was also a trend in ganciclovir recipients toward a survival benefit at 18 months (37% in the ganciclovir group and 45% of the patients in the placebo group had died), but this was not statistically significant (p=0.13).

A conflicting result on the effectiveness of oral ganciclovir for CMV prophylaxis was reported from the NIH-sponsored Community Programs for Clinical Research on AIDS (CPCRA) (97). In this study, patients with CD4 counts less than 100 cells/mL were eligible. As in study #1654, the endpoint was development of CMV disease. In contrast to study #1654, there was no significant difference between the ganciclovir arm and the placebo arm in the proportion of patients who died or developed CMV disease.

The difference in the results of the two studies can be explained perhaps by differences in study design, drug exposure, and study population. In study #1654, ophthalmologic examinations were required at baseline and every 2 months thereafter, regardless of whether symptoms of retinitis were present. In the CPCRA study, baseline ophthalmologic examination was not required in the absence of symptoms. Follow-up examinations were performed only if symptoms were reported. Therefore, asymptomatic retinitis may not have been detected in the CPCRA study.

The duration of drug exposure also differed in the two studies. The median duration of treatment for the blinded portion of the CPCRA study was 7.2 months, versus 8.7 months for study #1654. Based on preliminary results favoring treatment with oral ganciclovir, the Data and Safety Monitoring Board (DSMB) of the Division of AIDS (NIAID) recommended discontinuation of the placebo arm of study #1654. Shortly after, the DSMB recommended continuation of CPCRA 023, but study participants were offered the option of switching to treatment with oral ganciclovir.

The degree of immunosuppression of patients in the two studies also differed. Patients treated with oral ganciclovir in study #1654 had mean and median CD4 cell counts of 26 cells/ μ L

and 21 cells/ μL respectively, and 88% had CD4 cell counts of less than 50 cells/ μL . In contrast, those in the CPCRA study had mean and median CD4 cell counts of 44 cells/ μL and 35/ μL , and 65% had CD4 cell counts of less than 50 cells/ μL . Based on these demographic data, patients treated in study #1654 appear to have been more immunosuppressed and therefore were more likely to develop CMV disease. Consequently, the CPCRA study may not be powerful enough to bring out the differences between the groups.

Valaciclovir, a pro-drug of acyclovir, given as a high dose of 2 g by mouth, 4 times daily, was compared in a randomized trial to acyclovir given in a dose of either 400 mg by mouth, twice daily, or 800 mg by mouth, 4 times daily, for the prevention of CMV disease in CMV seropositive patients with CD4 count less than 100 mm^3 by the AIDS Clinical Trials Group (ACTG) (98). This study was terminated early because there was a trend of increased mortality in the valaciclovir arm ($p=0.06$). The reason for this trend in mortality is unknown. However, CMV disease occurred in 17.5% of acyclovir recipients and 11.7% of valaciclovir recipients ($p=0.04$).

New Developments

Intravitreal injection of cidofovir is also being studied in conjunction with oral probenecid. Doses higher than 20 μg have had unacceptable toxicity (mainly ocular hypotony). A single 20 μg injection appears to control CMV retinitis for about 2 months. There was some lowering of intraocular pressure, and a mild-to-moderate iritis developed in about 20% of eyes (99, 100). However, the formulation studied differs from that which is now available for intravenous use; the safe and effective dosage for intravitreal use has not been determined.

ISIS-2922 is a phosphorothioate anti-sense nucleotide complementary to CMV messenger RNA-encoding regulatory proteins. It is given only as an intravitreal injection once a week for 2–3 doses for induction and then every 2 weeks for maintenance. Ocular and systemic side effects were monitored immediately prior to the administration of each dose for the duration of treatment which exceeded 50 weeks in some patients. It has had apparent efficacy in patients intolerant of or unresponsive to intravenous ganciclovir or foscarnet, but can cause uveitis and a dose-related retinal toxicity (101).

Potentially more effective oral agents are also being tested. Valganciclovir is a pro-drug of ganciclovir. When given orally twice daily, valganciclovir has a bioavailability of 40%. It provides areas under the time/concentration curve of ganciclovir which are comparable to intravenous ganciclovir. Lobucavir is a new nucleoside analog with broad-spectrum *in vitro* activity against CMV and other herpes viruses, as well as HIV and hepatitis B viruses. Its oral bioavailability is 30–40% (102). The benzimidazole riboside compounds, 1263W94 (5,6-dichloro-2[isopropylamino]-1- β -L-ribofuranosyl-1H-benzimidazole) and BDCRB (5,6-dichloro-2-bromo-1- β -D-ribofuranosyl-1H-benzimidazole), are a new class of potent inhibitors of CMV replication. 1263W94 inhibits the accumulation of linear and high molecular-weight CMV DNA and is being tested in HIV-positive patients (103). BDCRB blocks a step necessary for packaging unit lengths of CMV DNA into the nucleoside. Neither of these drugs depends on the inhibition of the viral

DNA polymerase, which makes them attractive alternative agents for drug-resistant strains.

Currently, new methods of treating HIV with combinations of highly active retroviral agents including protease inhibitors enable an improvement in immune function and CD4 count. Indirectly, these may also delay the development of CMV disease or prevent reactivation of CMV retinitis (104, 105). This clinical observation is intriguing, but a controlled clinical trial is needed to confirm this result. A caveat is that patients on highly active antiretroviral therapy may also develop CMV retinitis even if CD4 counts exceed 200 (106).

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