Advances in the Management of AIDS-Related Cytomegalovirus Retinitis

Moderator: Henry Masur, MD; Discussants: Scott M. Whitcup, MD; Charles Cartwright, PhD; Michael Polis, MD; and Robert Nussenblatt, MD

Cytomegalovirus (CMV) retinitis, a common complication of the acquired immunodeficiency syndrome (AIDS), is increasing in frequency as patients infected with the human immunodeficiency virus (HIV) live longer. In recent years, the lifetime risk for CMV disease in HIV-infected persons has increased from 24.9% to 44.5%. Cytomegalovirus retinitis is usually diagnosed clinically: Almost all patients are CMV seropositive and have CD4+ counts less than 50 cells/mm^3. Specific diagnostic tests that use antigen detection or quantitation of circulating nucleic acid to detect CMV are being developed, but they have not been validated for routine clinical use. Such tests would help predict disease, diagnose acute retinitis, and monitor therapy.

Therapy with systemic agents, including intravenous ganciclovir, intravenous foscarnet, and intravenous cidofovir, is effective. However, it is cumbersome, costly, and associated with considerable toxicity, thereby encouraging investigation of other therapeutic approaches. Intravitreous injections with antiviral agents are effective, but the short half-life of available agents makes these injections inconvenient. Intracocular implants that slowly release ganciclovir have been effective for both acute therapy and long-term maintenance, but they need to be directly compared with intravenous and oral regimens to determine which regimen will optimally maximize convenience, preserve vision, and improve survival. Cytomegalovirus retinitis could be prevented by improved antiretroviral therapies or by immune-based therapies that would prolong the time during which patients remain immunocompetent. Once patients become immunologically susceptible to CMV end-organ disease (when their CD4+ counts decrease to <50 cells/mm^3), specific chemotherapy with oral ganciclovir is promising, but the cost, inconvenience, toxicity, and conflicting reports of efficacy associated with this strategy mean that it needs careful assessment before it can be considered standard treatment. Management of CMV retinitis is on the verge of major changes. In the next few years, improvements in diagnostic, therapeutic, and preventive tools should reduce morbidity and mortality from this disease.


Dr. Henry Masur (Critical Care Medicine Department, Clinical Center, National Institutes of Health [NIH], Bethesda, Maryland): In patients with human immunodeficiency virus (HIV) infection and severe immunosuppression, cytomegalovirus (CMV) has an unusual predilection for causing retinal disease. Cytomegalovirus can cause pulmonary disease, gastrointestinal disorders, or disabling central or peripheral neurologic dysfunction and may have other manifestations; however, retinal disease (although it occurs rarely in bone marrow or solid organ transplant recipients) is by far the most common clinical manifestation of CMV for patients with HIV. Cytomegalovirus retinitis causes progressive retinal destruction and is particularly feared by patients because loss of vision and cumbersome, inconvenient, and expensive therapies can greatly affect their lifestyles.

Cytomegalovirus is a DNA-containing, enveloped virus that is acquired by congenital, sexual, or person-to-person routes; cases are also occasionally caused by receipt of blood products or organ transplants. Cytomegalovirus has been acquired and has become latent in more than 90% of homosexual men and more than 70% of intravenous drug abusers (1, 2). One autopsy study reported that 81% of HIV-infected patients had developed clinical or pathologic evidence of CMV disease by the time they died; 32% had CMV retinitis (3). In a prospective clinical observational study, 4.5% of patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related conditions and CD4+ counts less than 200 cells/mm^3 developed CMV disease in 1 year, and 15.5% developed it within 2 years (4).

For patients with CD4+ counts less than 100 cells/mm^3, the probability for developing CMV disease within 2 years was 21.4% (4). The frequency of CMV retinitis is increasing as other opportunistic infections are being managed more effectively;

See related article on pp 98-103 and editorial comment on pp 144-145.
CMV retinitis was recorded as an AIDS-defining disease in 3.1% of patients in the era before widespread pneumocystis prophylaxis and in 9.4% of patients during the period of routine prophylaxis. The lifetime risk for CMV disease was 24.9% during the former period and 44.9% in the latter period (5). In a 1987 report (6), 5.2% of deaths in patients with AIDS were attributed to CMV disease; this percentage was 9.9% in 1992. Thus, CMV disease, especially CMV retinitis, is a common manifestation of AIDS that has been increasing in frequency during the first 15 years of the AIDS epidemic in North America.

Management of CMV retinitis is on the verge of rapid changes that could make recognition, therapy, and prevention more effective and more convenient. This Clinical Staff Conference reviews recent developments that offer potential for improving management of this disease.

**Diagnosis, Screening, and Prognosis**

Dr. Scott M. Whitcup (National Eye Institute [NEI], NIH): Cytomegalovirus retinitis is diagnosed predominantly on the basis of its clinical appearance. It characteristically appears as a patch of fluffy white retinal infiltrate with several areas of retinal hemorrhage (Figure 1). However, CMV retinitis can also have a granular appearance with little associated hemorrhage; in this form, it can be more difficult to recognize. Without treatment, both forms of CMV retinitis progress to retinal necrosis and permanent loss of vision. Retinitis usually spreads at the border of an area of previously infected retina; thus, borders need to be carefully assessed. New areas of retina may become involved as well.

Despite treatment, CMV retinitis progresses over time. Because it is often difficult to determine whether progression has occurred, retinal photographs taken at subsequent examinations can be an extremely useful adjunct to clinical examination. In clinical trials in which progression is the primary end point, progression should be assessed by having graders read masked retinal photographs.

Patients with CMV retinitis may have floaters, flashes of light, blurred vision, or blind spots. Further, when the macula or optic nerve is involved, patients may note severe loss of vision. Cytomegalovirus retinitis can also cause retinal detachment, which can be difficult to repair and is often associated with poor visual prognosis (7–10). Although patients with detachments note floaters and flashes of light, they often describe their vision loss as a curtain coming down over the eye. Some patients with CMV retinitis are asymptomatic, especially when the disease is limited to the peripheral retina.

Children rarely complain of symptoms, even when vision loss is profound, and diffuse blinding retinitis is often seen at initial diagnosis.

Cytomegalovirus retinitis can be clinically associated with mild vitritis (inflammatory cells in the vitreous) or no inflammation, but severe vitritis that obscures the retina suggests other conditions, such as toxoplasmosis (Figure 2). Mild anterior uveitis (inflammation in the anterior chamber of the eye) can also occur, and retinal vasculitis manifested by sheathing of the retinal vessels is seen in many patients with CMV retinitis.

Several conditions affect the posterior segment of the eye in patients with AIDS. Careful clinical examination can distinguish lesions that affect the retina from those limited to the choroid. Table 1 lists the choroidal and retinal diseases associated with AIDS. Because CMV retinitis primarily involves the retina, the diagnostic differentials of CMV retinitis include other disorders that affect the layers of the
Table 1. Retinal and Choroidal Pathology in Patients with Human Immunodeficiency Virus Infection

<table>
<thead>
<tr>
<th>Diseases involving the retina</th>
<th>Human Immunodeficiency Virus infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus infection</td>
<td>Cytomegalovirus infection</td>
</tr>
<tr>
<td>Herpes simplex virus infection</td>
<td>Herpes simplex virus infection</td>
</tr>
<tr>
<td>Herpes zoster virus infection</td>
<td>Herpes zoster virus infection</td>
</tr>
<tr>
<td>Treponema pallidum infection</td>
<td>Treponema pallidum infection</td>
</tr>
<tr>
<td>Toxoplasma gondii infection</td>
<td>Toxoplasma gondii infection</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Human immunodeficiency virus infection</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Infections involving the choroid</td>
<td>Infections involving the choroid</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>Pneumocystis carinii</td>
</tr>
<tr>
<td>Atypical mycobacteria</td>
<td>Atypical mycobacteria</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Cryptococcus neoformans</td>
</tr>
</tbody>
</table>

retina. The most common cause of ocular disease, HIV retinopathy, occurs in as many as 100% of patients with AIDS during the course of illness (11-13). Cotton wool spots induced by HIV infection are nerve fiber layer infarctions that can resemble early CMV retinitis, but these infarctions resolve over time without therapy. On rare occasions, intraocular lymphoma can cause a type of retinitis similar to CMV retinitis (14), but the lesions are usually associated with cerebral or cerebellar involvement. Many other infectious diseases, including toxoplasmosis (Figure 2) (15), syphilis, herpes zoster (16), and herpes simplex retinitis (17), can involve the retina and must be distinguished from CMV because their therapies are different.

Because CMV retinitis is rare in persons with CD4+ counts greater than 100 cells/mm³, these counts can be useful in determining when to screen patients for this condition (18). Screening should include measurement of visual acuity and a retinal examination done through dilated pupils. We do screening examinations every 6 months in patients with CD4+ counts between 50 and 100 cells/mm³ and every 3 to 4 months when CD4+ counts decrease to less than 50 cells/mm³. Ophthalmologic examination is also done in patients with new visual symptoms and in those who have CMV infection elsewhere in the body. However, it should be noted that although prompt diagnosis and early treatment appear to limit such complications as retinal detachment and the involvement of sight-critical structures (such as the optic nerve and macula), the benefits of routine screening examinations in preserving lifetime vision have not been proven in a randomized clinical trial.

In terms of prognosis, studies have shown that many patients who receive early therapy for CMV retinitis can maintain useful vision throughout the course of illness. When the disease is detected and treated before the optic nerve and macula become involved, the visual prognosis for patients with CMV retinitis is good. In patients randomly assigned to receive ganciclovir or foscarnet in the

Studies of the Ocular Complications of AIDS (SOCA I) trial (19), visual acuity was 20/40 or better in at least one eye in 88% of patients 6 months after therapy was begun. Bilateral disease developed in 17% of patients, but loss of visual field was about 30° per month in all patients. Poor visual prognosis was associated with low visual acuity at baseline, CD4+ T-cell counts less than 14 cells/mm³, and extended therapy.

Laboratory Diagnosis

Dr. Charles Cartwright (Clinical Pathology Department, Clinical Center, NIH): Most persons positive for HIV are seropositive for CMV, and some have been reported to have persistently elevated IgM and IgG titers (1, 20). Thus, testing for CMV antibody is helpful only if a patient is shown to be seronegative. Cytomegalovirus disease is extremely unlikely to occur in seronegative patients, although this is theoretically possible because some patients with recent primary infection (or, on rare occasions, patients with chronic infection) might not have produced antibodies.

Infectious virus can frequently be recovered from various sources in HIV-positive patients with low CD4+ counts (typically <100 cells/mm³); these sources include leukocytes, saliva, respiratory secretions, and urine. Patients with positive cultures, especially positive blood cultures, have a higher risk for CMV end-organ disease than do persons with negative cultures (21-23). Because the positive and negative predictive value of blood cultures in HIV-positive patients tends to be low, the value of blood cultures is questionable. Salmon and colleagues (21) determined that only 50% of viremic patients developed end-organ disease attributed to CMV during a 12-month follow-up period and that 9% of those who were nonviremic were diagnosed with CMV disease during the same 12 months. Similar results were obtained in an investigation by Zurlo and colleagues (22): Thirty-five percent of viremic patients and 15% of nonviremic patients, all with CD4+ counts of less than 200 cells/mm³, developed CMV disease in the subsequent 6 months.

Given the poor predictive value of viral culture, much effort has been devoted to developing alternative approaches for monitoring CMV activity. The use of monoclonal antibody–based stains in the nuclei of infected polymorphonuclear leukocytes to detect a CMV-specific 65-kd matrix protein (pp65) has been shown to be a highly sensitive and specific method of assessing CMV infection (24, 25). This assay has the added benefit of being quantitative; results are typically enumerated as infected cells per 2 x 10⁶ neutrophils. Unfortunately, little has been
published on the clinical utility of this assay in the diagnosis of CMV retinitis in patients with AIDS. In a recent report by Francisci and colleagues (26), 82% of patients with AIDS and CMV disease were antigenemic (only about 20% were culture positive). However, 25% of patients in whom disease was excluded also had positive results on antigen assays, which reflects the high sensitivity of this assay. It is interesting to note that these authors presented tantalizing preliminary data suggesting that degree of antigenemia may be a useful prognostic indicator for the development of CMV disease in patients with AIDS. Four of 6 patients with more than 100 antigen-positive cells and no concomitant evidence of CMV disease subsequently developed such disease within 3 months, although only 3 of 10 patients with a positive cell count of 1 to 50 subsequently developed the disease. No nonantigenemic persons developed CMV disease during the follow-up period. If this finding can be substantiated in a larger study, monitoring levels of CMV antigen in neutrophils could identify a subpopulation of HIV-positive patients with low CD4+ counts who are at imminent risk for CMV disease. In its current form, however, this assay is extremely labor intensive and is thus impractical for routine use.

In efforts to reach the ultimate goal—a laboratory-based assay to rapidly and accurately identify HIV-positive patients at greatest risk for CMV retinitis before the onset of symptoms—the value of molecular-based techniques for detecting the virus has been extensively examined. Attention has focused primarily on the use of polymerase chain reaction (PCR)-based amplification assays for detecting viral DNA in blood components, particularly leukocytes (27-32). All investigations thus far have shown that PCR is the most sensitive technique currently available for the detection of systemic CMV infection. The fundamental problem is that the exquisite sensitivity of the technique results in detection of considerably more patients with asymptomatic infection than do either culture or antigen detection (27, 28). Interest has recently shifted, therefore, to two questions. Do differences exist in the amount of CMV DNA in the blood, leukocytes, or plasma of asymptomatic and symptomatic patients? If so, should quantitative PCR be used to differentiate high- and low-risk populations? Rasmussen and colleagues (29) showed that quantitative differences existed in the amount of CMV DNA present in the leukocytes of symptomatic and asymptomatic persons, that DNA levels strongly correlated with immunologic status, and that onset of disease was preceded in some patients by an increase in CMV DNA levels. It should be noted, however, that levels of CMV DNA in symptomatic patients varied widely and that almost 50% of these patients had either no detectable CMV DNA or levels of CMV DNA that were no higher than those found in asymptomatic persons. Using a semiquantitative PCR assay, Drouet and colleagues (30) found a correlation between high CMV DNA levels and incidence of disease. In that small study, three patients with retinitis had persistently high PCR signals both before and at the time of diagnosis, and an increase in CMV DNA signal preceded diagnosis by 3 to 8 weeks. Further, no patients free of CMV disease had persistently elevated CMV DNA levels. Griffiths and colleagues (31) have also shown a high predictive value for CMV PCR, but only results from a qualitative assay have been reported.

In addition to the potential use of PCR in a diagnostic setting, the value of the disappearance of leukocyte or serum CMV DNA positivity as a measure of therapeutic response has been examined (33, 34). Data have generally shown that loss of the PCR signal from blood correlates strongly with a positive response to therapy. Given this finding and the enhanced sensitivity of PCR compared with other detection methods, it seems likely that one application of DNA-based detection of CMV infection will be to help clinicians assess the success of therapeutic intervention in symptomatic patients.

Data obtained from studies examining culture-, antigen-, and DNA-based detection of CMV appear to tentatively support the notion that sensitive, quantitative assessment of systemic CMV activity (through antigen or DNA detection) will enable the laboratory-based identification of HIV-positive patients at greatest risk for CMV retinitis. However, more clinical validation clearly must be obtained before a recommendation can be made about the precise utility of either quantitative antigen or DNA-based assays. If the clinical value of monitoring the systemic burden of CMV in patients with HIV can be substantiated, the impending availability of commercial, high-throughput, nucleic acid amplification-based test systems promises to make this a viable option for many diagnostic laboratories. The goal of using laboratory results as a key component in predicting, diagnosing, and treating CMV disease may finally be realized (35).

Systemic Treatment

Dr. Michael Polis (National Institute of Allergy and Infectious Disease, NIH): Systemic therapy for CMV retinitis has been limited to two agents: ganciclovir, available in intravenous and oral formulations, and foscarnet, available only in intravenous form. Ganciclovir, which has been available in the parenteral formulation since 1988, is a nucleoside analogue whose major toxic side effect is myelosup-
pression (36, 37). The recommended dosage in adults with normal renal function is 5 mg/kg of body weight twice a day for 14 to 21 days until the retinitis is quiescent followed by 5 mg/kg once a day for life or until the retinitis progresses. Ganciclovir must be used with caution in persons with neutropenia or thrombocytopenia, but preserving vision is often judged more important than maintaining granulocyte counts greater than arbitrary levels. The use of ganciclovir in combination with zidovudine or other myelosuppressive agents may necessitate the use of colony-stimulating factors to counter granulocytopenia.

Foscarnet, licensed in 1991, is a simple pyrophosphate whose major side effect is renal toxicity (38, 39). The drug is administered intravenously at a dosage of 60 mg/kg every 8 hours or 90 mg/kg every 12 hours for 14 to 21 days until the retinitis is quiescent. This is followed by 90 to 120 mg/kg once a day for life or until the retinitis progresses. Most persons currently use the recently approved twice-daily induction regimen because of its greater convenience. The use of foscarnet with other agents that cause renal insufficiency, such as amphotericin B or aminoglycosides, should be avoided. Foscarnet is an anionic compound that binds divalent cations—particularly calcium and magnesium—and often causes irregularities in these electrolytes and in inorganic phosphate and potassium. Other agents that cause hypocalcemia in persons with HIV, such as parenteral pentamidine, should be used with foscarnet only with extreme caution. Schema for the management of the common problems related to ganciclovir and foscarnet toxicity have been proposed (39).

Results of a randomized clinical trial (40) comparing intravenous ganciclovir and intravenous foscarnet have shown that the therapies are equally able to limit the progression of CMV retinitis in persons with HIV. Although the median times from the institution of induction therapy to initial progression of CMV retinitis was 56 days in persons receiving ganciclovir and 57 days with oral ganciclovir once a day and 63 patients were randomly assigned to receive 5 mg/kg of intravenous ganciclovir once a day and 63 patients were randomly assigned to receive 1000 mg of oral ganciclovir three times a day. By using masked assessment of fundus photographs, the mean time to progression from the start of maintenance therapy was determined to be 62 days with intravenous ganciclovir and 57 days with oral ganciclovir. The median time to progression was 49 days with intravenous ganciclovir and 29 days with oral ganciclovir (44). These results were considered sufficient to warrant licensing oral ganciclovir as a maintenance regimen. Table 3 compares the clinical efficacy of oral ganciclovir with that of other regimens.

It is important to determine the incidence of resistance in persons receiving oral ganciclovir. In

### Table 2. Regimens for Acute Induction of Cytomegalovirus Retinitis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosage</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>Intravenous</td>
<td>5 mg/kg body weight twice daily for 14 to 21 d</td>
<td>30 min infusion time</td>
<td>36, 39, 40</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Intravenous</td>
<td>5 mg/kg weekly for 2 wks</td>
<td>Requires operative procedure;</td>
<td>42</td>
</tr>
<tr>
<td>Cidofovir (ocular insert)</td>
<td>Intracocular</td>
<td>1 µg/h</td>
<td>Requiring operative procedure;</td>
<td>41</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Intravenous</td>
<td>60 mg/kg three times daily or 90 mg/kg twice daily for 14 to 21 d</td>
<td>2 h infusion time after 1 h saline load (500 cc normal saline)</td>
<td>38-40</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Intravenous</td>
<td>1 µg/h</td>
<td>Requiring operative procedure;</td>
<td>41</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Intravenous</td>
<td>60 mg/kg three times daily or 90 mg/kg twice daily for 14 to 21 d</td>
<td>Requires operative procedure;</td>
<td>41</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Intravenous</td>
<td>5 mg/kg weekly for 2 wks</td>
<td>Requires operative procedure;</td>
<td>41</td>
</tr>
</tbody>
</table>

8.5 months for ganciclovir (40). It has been proposed that this difference is due to the anti-HIV activity of foscarnet. Whether the difference is real and whether it is relevant in an era of combination antiretroviral regimens remain to be determined. This reported advantage for patients treated with foscarnet should be a minor factor in determining the optimal therapy for induction and maintenance therapies for CMV retinitis. More important considerations are ease of administration and toxicity (Table 2).

The availability of an oral formulation of a drug with activity against CMV offers the potential for greatly enhanced convenience in the administration of therapy. The bioavailability of the oral formulation of ganciclovir ranges from 2.6% to 7.3% with a serum half-life of 3.0 to 7.3 hours (43); the serum half-life of the intravenous formulation is 2.5 to 3.6 hours. Although the maximum concentration of the 1000-mg dose, 0.5 µg/mL, approaches the IC₅₀ of most clinical CMV isolates (43), it is not nearly as high as the maximum concentration of 9.5 µg/mL achieved with 5 mg/kg of intravenous ganciclovir. Larger and more frequent oral doses have not produced substantially higher serum concentrations.

Oral ganciclovir has not been studied as initial or induction therapy but has been assessed as maintenance therapy. In one study of persons with newly diagnosed, clinically inactive CMV retinitis, after the 21-day ganciclovir-induction regimen, 60 patients were randomly assigned to receive 5 mg/kg of intravenous ganciclovir once a day and 63 patients were randomly assigned to receive 1000 mg of oral ganciclovir three times a day. By using masked assessment of fundus photographs, the mean time to progression from the start of maintenance therapy was determined to be 62 days with intravenous ganciclovir and 57 days with oral ganciclovir. The median time to progression was 49 days with intravenous ganciclovir and 29 days with oral ganciclovir (44). These results were considered sufficient to warrant licensing oral ganciclovir as a maintenance regimen. Table 3 compares the clinical efficacy of oral ganciclovir with that of other regimens.

It is important to determine the incidence of resistance in persons receiving oral ganciclovir. In
persons who received intravenous ganciclovir for more than 3 months, only 8% excreted CMV isolates resistant to ganciclovir in their urine (50). More recent data from a trial of prophylactic oral ganciclovir (51) showed an overall prevalence of resistance of less than 1% after a mean of 10 months of preventive treatment. It is therefore most likely that progression of retinitis despite therapy with oral or intravenous ganciclovir results from the inability to maintain adequate levels of drug in serum than to the development of resistance. With the approval of oral ganciclovir for maintenance therapy for CMV retinitis, it will be difficult to do a randomized trial to determine the absolute utility of oral ganciclovir for long-term suppression. Trials are in progress to determine the efficacy of higher doses.

Because of the predictable progression of CMV retinitis that occurs despite currently available regimens, the combined use of ganciclovir and foscarnet has been actively investigated (52–54). Fortunately, the toxicity profiles of ganciclovir and foscarnet are very different. Using these agents together for CMV disease that is resistant to both agents individually has resulted in no more toxicity than has using each drug alone. In one study (52), 10 patients with AIDS and progressive CMV disease who were treated serially with both agents for a median of 330 days were subsequently treated with both agents combined for a median of 80 days; 9 of 10 patients responded. A CMV retinitis retreatment trial (49) sponsored by the NEI has recently been completed; it studied persons with persistently active or relapsed CMV retinitis. Data from the trial, in which patients were randomly assigned to standard treatment with ganciclovir, foscarnet, or a combination of the two, show that combination therapy (intravenous ganciclovir, 5 mg/kg daily, and intravenous foscarnet, 90 mg/kg daily) produces a longer median remission (4.3 months) than either ganciclovir alone (2.0 months) or foscarnet alone (1.3 months). The combination maintenance regimen was associated with less loss of visual field than was either monotherapy, but combination therapy did have a greater negative effect on quality-of-life measures (49).

Intravenous foscarnet and ganciclovir are both effective in decreasing the rate of progression of CMV retinitis in persons with HIV. Oral ganciclovir may be considered for maintenance therapy in persons with limited, non-sight-threatening retinitis. A combination of both agents is a logical option for persons with persistently active or relapsed retinitis that occurs after the use of either agent individually.

Cidofovir, (S)-1-[3-hydroxy-2-[(phosphonylmethoxy)propyl]cytosine (HPMPC), is a nucleotide analogue with activity against all human herpesviruses; it has a prolonged intracellular half-life, suggesting that infrequent administration is possible (42, 55). Its major side effect is renal toxicity, and administration of it requires saline hydration during infusion and coadministration of probenecid around the time of infusion. In a study that used the standard design for peripheral retinitis studies (38) and masked retinal photographs to document progression of retinitis as the end point, 48 persons were randomly assigned to receive either deferred therapy or 5 mg/kg of intravenous cidofovir weekly for 2 weeks then once every 2 weeks (47). The median time to progression was 120 days in persons assigned to receive cidofovir and 22 days for persons receiving deferred therapy.

### Table 3. Regimens for Chronic Suppression of Cytomegalovirus Retinitis*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Time to Relapse</th>
<th>Survival after Diagnosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial episode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Intravenous</td>
<td>5 mg/kg body weight daily</td>
<td>47–70 62–84</td>
<td>8.5</td>
<td>36, 40, 44</td>
</tr>
<tr>
<td>Oral</td>
<td>1 g three times daily</td>
<td>50 78 ND</td>
<td></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Injection</td>
<td>400 μg/kg</td>
<td>56 ND</td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Intravenous Insert</td>
<td>1 μg/h release</td>
<td>226 ND</td>
<td></td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Intravenous</td>
<td>90–120 mg/kg daily</td>
<td>31–59 72</td>
<td>12.6</td>
<td>38–40</td>
</tr>
<tr>
<td>Injection</td>
<td>2400 μg/kg</td>
<td>ND ND</td>
<td></td>
<td></td>
<td>ND 46</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Intravenous</td>
<td>5 mg/kg every 2 weeks</td>
<td>120</td>
<td>ND</td>
<td>42, 47</td>
</tr>
<tr>
<td>Injection</td>
<td>20 μg</td>
<td>ND ND</td>
<td></td>
<td></td>
<td>ND 48</td>
</tr>
<tr>
<td><strong>Relapsed episodes only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Intravenous</td>
<td>10 mg/kg per day</td>
<td>60</td>
<td>9.0</td>
<td>49</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Intravenous</td>
<td>120 mg/kg per day</td>
<td>40</td>
<td>8.4</td>
<td>49</td>
</tr>
<tr>
<td>Both</td>
<td>Intravenous</td>
<td>130</td>
<td>8.6</td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

* ND = no for insufficient data.
† After initial induction. Estimates from randomized, controlled trials using photographic end points, or, in absence of randomized trials, best open trial with days expressed as time from initiation of induction therapy.
‡ Intracocular injection.

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Several new drugs are in the advanced phases of clinical testing. A neutralizing, non–complement-dependent monoclonal CMV antibody has been used as adjunct therapy with ganciclovir and foscarnet. Preliminary data suggest that time to progression, determined by clinical examination, exceeded 200 days; this period was substantially longer than that for controls treated with ganciclovir or foscarnet alone (56). Two trials are currently evaluating this adjunct therapy in combination with ganciclovir or foscarnet.

Polyclonal anti–CMV immune globulin has been shown to attenuate the primary CMV disease associated with kidney transplantation. In a pilot study (57) done to evaluate the efficacy of this agent for prophylaxis against CMV disease among persons with HIV, patients with CMV viruria who were given intravenous polyonal anti–CMV immune globulin showed no decrease in qualitative excretion of CMV in the urine or in the ability to culture CMV from the blood. They developed CMV disease at a rate similar to that of controls. Trials are in progress to evaluate this agent as adjunctive therapy for CMV disease in transplant recipients and for CMV retinitis in persons with AIDS.

Any discussion of treatment would be incomplete without a mention of cost. The yearly cost of drugs with which to treat CMV retinitis ranges from approximately $9000 to more than $20 000. Adding the costs of treatment administration, nursing care, physician monitoring, maintenance of a chronic indwelling catheter, and other health care brings the yearly total for treating CMV retinitis to at least $50 000; it is often more than $100 000. Although considerable progress has been made during the past 14 years, more convenient, less costly, and more effective therapies are clearly needed.

Local Therapy

Dr. Robert Nussenblatt (NEI, NIH): Although CMV infection in patients with HIV is systemic, ocular disease may be its only clinically apparent manifestation. It is logical to treat CMV infection with systemic therapy, but, to date, it is not clear that survival or quality of life are more improved by systemic as opposed to local therapies.

Systemic therapy for CMV disease has limited efficacy and effectiveness. Induction regimens almost always halt the spread of retinal infections and convert areas of active inflammation to inactive retinal scars, but maintenance regimens are expensive and cumbersome, requiring either indwelling intravenous access with time-consuming infusions or consumption of a dozen pills a day. Moreover, while patients are receiving maintenance regimens of ganciclovir or foscarnet, CMV retinitis reoccurs within a mean of 50 days after the institution of maintenance doses (Table 3). Local therapy for CMV retinitis (direct instillation of drug into the globe) would preclude the need for chronic indwelling catheters and long infusion times and would eliminate the systemic toxicity that occurs with intravenous maintenance. In addition, local therapy would preclude the expense, compliance problems, and toxicity that occur when an oral ganciclovir maintenance regimen is used.

A local intracocular therapeutic approach takes advantage of the anatomic region of the eye known as the pars plana, which is a few millimeters behind the corneal limbus. The pars plana is the region through which a surgical instrument, an implant, or a needle can be used to penetrate the vitreous without causing retinal detachment.

Local Injections

The drug that has been most used for intraocular injection is ganciclovir. It is usually given in a volume of 0.1 mL after proper local antisepsis and anesthesia have been applied to the globe. Injections are initially given two to three times a week for 2 to 3 weeks, and then a once-a-week “maintenance” schedule is started (58). In a report by Cochereau-Massin and colleagues (45), 64 eyes received a total of 710 intravitreous injections of ganciclovir (400 μg per injection). After a mean of 6.6 injections, all but one induction course had resulted in initial control of the retinitis. However, the 8-week relapse rate was 53%, and disease developed in the other eye in 11% of patients and at a nonocular site in 16%. During this treatment period, five retinal detachments and two intraocular hemorrhages also occurred. Cataracts and endophthalmitis are also possible complications, although they did not occur in this study. Thus, this regimen had limited long-term success and suggested that higher doses or more frequent injections were necessary.

Foscarnet has also been given intravitreously, although few patients have been treated with this method (46). Individual injections of 2400 μg have been given. Results have been similar to those reported with ganciclovir.

Local injections of the novel agent ISIS-2922, a phosphorothioate nucleotide that is complementary to viral messenger RNA–encoding regulatory proteins, have been assessed as a maintenance regimen in an uncontrolled series (59). In five of eight patients, ocular infection appeared to be controlled at doses from 150 to 300 μg. However, instillation of this drug appears to produce peripheral retinopathy (60). More investigations are needed to assess different doses, schedules, and product formulations.
Cidofovir has been given intravitreously. In one series of 17 patients (24 eyes) treated with a single 20-μg dose of cidofovir given once through intravitreous injection, the median time to progression was 55 days (48). The decrease in intraocular pressure from baseline that was noted both 2 and 4 weeks after injection was significant, but it was not associated with clinically apparent visual loss. (A marked and sustained decrease in intraocular pressure can be associated with loss of ocular viability.) Also, mild to moderate iritis developed in about 20% of eyes receiving this implant and a mean time to progression of 133 days. Martin and colleagues (41) recently reported the results of a randomized study, done at the NEI and at Emory University (Atlanta, Georgia), that assessed these devices as initial therapy for 26 patients who had AIDS and CMV retinitis involving the periphery of the retina. Patients either received immediate therapy with a ganciclovir sustained-release device (1 μg/h release rate) or had therapy deferred until progression was documented. The mean time to progression was 15 days in the patients randomized to deferred therapy and 226 days in those receiving the implant. The group that received the operation had no cases of endophthalmitis, but 18% of the operated eyes had retinal detachments within several months of the procedure. It is difficult to ascribe all of these detachments to the surgical procedure itself, because 13% to 50% of patients with CMV retinitis develop retinal detachments during the first year of systemic therapy. During the course of the study, no systemic therapy for CMV was administered, and 50% of patients had developed contralateral CMV within 203 days of study entry. Systemic manifestations of CMV disease, such as pneumonitis or colitis, were seen in 31% of these 26 patients. Nine patients ultimately received intravenous ganciclovir therapy. The median survival of patients in this study was 9.8 months; that of patients enrolled in a previous intramural study that used systemically administered fosfomycin was 13.5 months (38). A subsequent multicenter study (62) yielded similar results.

Thus, local therapy for CMV retinitis offers the potential for more convenient, more effective, and less toxic management. The relative benefits of this approach, especially in a community-based setting, need to be carefully addressed to develop a therapeutic strategy that maximizes convenience and survival and preserves vision.

**Prevention**

Dr. Masur: Because CMV disease is among the most frequent and most devastating complications of HIV infection, it deserves high priority. Primary prevention—prevention of initial CMV infection—is a logical strategy for the small fraction of HIV-infected persons who are seronegative for CMV. Avoiding unprotected sexual contact with CMV-positive persons, precluding exposures at daycare centers to children who are likely to be shedding CMV, and preventing transfusion with unfiltered CMV-positive blood products are logical strategies (63). Whether patients who already harbor latent CMV infection develop disease as a result of newly introduced, superimposed strains as well as by reactivation of latent infection is uncertain. Thus, whether primary prevention would benefit CMV-seropositive persons is unknown.

Patients who develop CMV retinitis usually are CMV seropositive and have CD4+ counts less than 50 cells/mm³. Another potential strategy for reducing the frequency of retinitis is to prevent the CD4+ count from reaching such low levels. Although they may slow the decline in CD4+ counts, aggressive antiretroviral therapies probably cannot prevent deterioration indefinitely. In many patients, interleukin-2 therapy can increase CD4+ counts substantially and sustain them at normal or supranormal levels for months or years before counts decrease to less than 200 to 300 cells/mm³ (64). Whether this therapy will be useful for preventing or reducing the incidence of opportunistic infections remains to be determined.

As Dr. Cartwright indicates, laboratory markers to predict which patients with CD4+ counts less than 50 cells/mm³ are most likely to develop CMV retinitis would be useful. In one study of patients who had either CD4+ counts less than 50 cells/mm³ or AIDS and CD4+ counts less than 100 cells/mm³, the median time to development of CMV disease was 358 days, a long interval during which to take costly, inconvenient, and potentially toxic drugs (65, 66). A reliable laboratory marker that precedes CMV end-organ disease would allow patients to avoid prophylaxis for many months and would spare...
them inconvenience, toxicity, and cost. Unfortunately, no such marker has been developed; blood or urine cultures have very low predictive values, and quantitative antigen or nucleic acid tests, although promising, are not yet validated.

Chemioprophylaxis, ideally done using an agent that is highly effective, safe, easy to administer, and inexpensive, is a reasonable option. Oral agents, such as acyclovir, valacyclovir, and famciclovir; long-acting parenteral agents, such as cidovir; and local agents or devices are now available as investigational or approved approaches. The most extensive data are available for oral ganciclovir, the only drug currently approved by the Food and Drug Administration for prophylaxis of CMV in patients with AIDS. In the first randomized, prospective, double-blind study to be completed (66), 774 patients with low CD4+ counts were randomly assigned to receive either oral ganciclovir (1 g orally, three times daily) or placebo. Cytomegalovirus disease, retinitis, and colitis occurred in 30%, 20%, and 10%, respectively, of patients receiving placebo but in only 16%, 10%, and 3%, respectively, of patients treated with ganciclovir. Also, less zone-1 disease (within 1500 μm of the optic nerve head) and a trend toward improved survival were seen in patients in the oral ganciclovir group (65, 66). Specific toxicities that were more common in the ganciclovir group included neuropathy, granulocytopenia, and anemia, and patients treated with ganciclovir were more likely to have received granulocyte colony-stimulating factor or erythropoietin. Little evidence showed that oral ganciclovir caused development of ganciclovir-resistant isolates (51), and this study concluded that oral ganciclovir is a highly effective prophylactic regimen with only modest toxicity.

Oral ganciclovir has some disadvantages. The recommended daily dose is 12 capsules, which can be difficult to tolerate. The annual wholesale cost of the drug is $14 000; if granulocyte colony-stimulating factor or erythropoietin is also used, the cost of therapy is substantially higher. Oral ganciclovir has also been reported to increase didanosine absorption dramatically if the two drugs are taken together, which may enhance the toxicity of didanosine (67). Also, it has not been conclusively shown that oral ganciclovir prophylaxis results in better long-term preservation of vision or survival than does careful clinical monitoring and intervention.

A recently completed study (68) failed to show that oral ganciclovir is beneficial and complicates the issue of whether oral ganciclovir should be used. In this study of 994 patients, prophylaxis with oral ganciclovir compared with placebo provided no benefit in preventing CMV disease, CMV retinitis, or death. The efficacy of oral ganciclovir was not statistically significantly better than placebo, although there was a trend suggesting benefit for oral ganciclovir. The entry criteria in this study differed from those of the previous one (66), and ophthalmologic examinations were done only when patients were symptomatic rather than routinely at study entry and at predetermined intervals. It is not clear why these two studies had such different results.

Thus, a drug that has been shown to reduce the incidence of CMV disease is available, but there are conflicting data about its efficacy and decided disadvantages to its use. The U.S. Public Health Service—Infectious Disease Society of America (69) recommend that prophylaxis with oral ganciclovir be considered an option for patients who can comply with and afford the regimen but that it should not be considered a “standard of care” like antineuromyocystis prophylaxis. In 1996, that seems to be a reasonable posture to maintain. Intermittent use of cidovir, a long-acting parenteral drug, and use of newer oral agents, such as famciclovir and valacyclovir, need to be assessed.

Conclusion

Dr. Masur: During the second half of this decade, CMV will probably become increasingly important as a cause of morbidity and mortality among patients with HIV. Quantitative diagnostic tests are likely to become available to enable better delineation of the interval during which patients are most likely to develop CMV disease and to determine how well patients respond to therapy. A growing number of drugs for oral, intravenous, and local therapy are also being developed and will probably be licensed in 1996, increasing the likelihood that this disease can be managed more efficiently, effectively, and safely. However, achieving this goal will require all the skill, knowledge, and cooperation of the primary care giver, the ophthalmologist, and the health care team, and the economic barriers to widespread use of these therapies will need to be overcome.

Requests for Reprints: Henry Masur, MD, Critical Care Medicine Department, National Institutes of Health, Building 10, Room 7D43, Bethesda, MD 20892.

Current Author Addresses: Dr. Masur: Critical Care Medicine Department, National Institutes of Health, Building 10, Room 7D43, Bethesda, MD 20892. Drs. Whitcup and Nussenblatt: National Eye Institute, National Institutes of Health, Building 10, Room 10N202, Bethesda, MD 20892. Dr. Cartwright: Nucleic Acids Division, Johnson & Johnson Clinical Diagnostics, Fourth Floor, Building 82, RL, Rochester, NY 14602-2117. Dr. Polis: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 10, Room 11C103, Bethesda, MD 20892.
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