



Cytomegalovirus

Cytomegalovirus

Cytomegalovirus (CMV) is the most common cause of sight-threatening infections in and one of the most common causes of death among people with HIV. Therapies are available to reduce the occurrence of CMV-disease. There have been some significant advances in CMV treatment over the past several years. Also, CMV disease has responded surprisingly well to the use of HAART (Highly Active Antiretroviral Therapy).

CMV is a member of the herpes family of viruses and is primarily a sexually transmitted disease, but it can also be transmitted from mother-to-child, through blood transfusions, by close personal contact and via organ transplantation. Initial infection with CMV in adults can be associated with mononucleosis-like symptoms (primarily fever and body aches) or without symptoms at all. Incidence of infection rises with age, and by adulthood, nearly half the population in developed countries is infected with this virus. CMV infection rates are much higher among people in high-risk groups for HIV infection: nearly 100% in gay men with about 25% – 40% actually developing CMV disease. The risk of developing CMV disease increases as CD4+ cell counts decline. It is believed that CMV disease is due to the reactivation of dormant CMV in immune compromised people. Up to 90% of people with HIV have evidence of CMV infection at autopsy, while about 10% is CMV considered to be the primary cause of death. However, CMV infections do not typically cause serious or life-threatening disease unless a person has a severely weakened immune system.

Symptoms

CMV can infect almost every part of the body. But in people with HIV, it seems to preferentially infect the eye in the form of CMV retinitis.

CMV Retinitis. The most common CMV-related condition in people with HIV is retinitis (inflammation of retina), characterized by a loss of visual acuity (sharpness) or blind spot in the eye. Left untreated, CMV retinitis will lead to blindness.

CMV Colitis. Colitis, or inflammation of the colon, is another CMV-related condition. People with this condition experience diarrhea, weight loss, loss of appetite and fever—symptoms which are so common in people with advanced HIV infection as to make it difficult to distinguish from other diseases of the intestinal tract. Diagnosis of CMV in the colon is difficult, and it requires at least 4–6 weeks to demonstrate that CMV is the cause of colitis and not other possible infections such as bacteria, fungi, parasites or other viruses. Because many of symptoms of CMV colitis are similar to symptoms of other opportunistic infections, it may be difficult to diagnose CMV colitis in its early stages. If you suspect that you have symptoms as outlined above, talk to your healthcare provider.

Encephalitis. CMV can also infect the brain and the nervous system in the form of inflammation of the brain (encephalitis) and inflammation of nerves (polyradiculopathy). Symptoms of encephalitis include dizziness, neurological dysfunction and seizures. Symptoms of polyradiculopathy include numbness and tingling (similar to that of peripheral neuropathy) and loss of muscle control. Again, some of these symptoms look exactly like those of other opportunistic infections, so sometimes CMV infection may be overlooked.

Diagnosis

The factors most associated with CMV disease are a CD4+ cell count of less than 50 and at least one other prior opportunistic infection. Recent studies have shown that anyone with detectable CMV levels using PCR (polymerase chain reaction test, the same technique used to detect HIV levels) or are either antigen or culture positive for CMV are at higher risk for developing CMV disease, though a measurable CMV PCR level, by itself, does not always correlate with active infection and symptomatic disease.

The diagnosis of CMV retinitis is usually confirmed by an ophthalmologist, a doctor who specializes in diseases of the eye. The ophthalmologist applies chemicals to dilate the eye, making it easier to look inside for evidence of lesions that may be caused by CMV. The diagnosis of CMV disease in other parts of the body is usually done by performing a biopsy of tissue from the suspected organ.

Prophylaxis

Preventing CMV has been a hotly debated topic because of conflicting study results.

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In one study, an oral formulation of ganciclovir (1000mg three times daily) was able to reduce the incidence of new CMV disease by 50% compared to placebo, while in another study, there was no clear difference between the two groups. In present form, oral ganciclovir is poorly retained by the body, probably accounting for its weak activity. However, it is obvious to almost all physicians that since the advent of HAART, the incidence of new CMV infection has dropped dramatically, on its own and without the use of CMV preventive therapies. The effectiveness of HAART in preventing new CMV disease is probably linked to its ability to raise and maintain CD4+ counts well above the level at which CMV disease begins to appear.

One of the fears around CMV preventative therapy is that if someone does develop CMV during therapy, then their treatment options are severely limited as a result of resistance and cross-resistance (resistance to one drug results in resistance to other drugs) to other CMV therapies. However, this does not appear to be the case based on results from a CMV prevention study that showed that people who received oral ganciclovir but developed CMV disease responded well to CMV treatment.

Treatment

Several therapies are approved for CMV disease treatment, including:

- daily intravenous (directly in the vein) infusions of ganciclovir (Cytovene)
- foscarnet (Foscavir)
- ganciclovir implant (Vitrasert, a device containing ganciclovir that is surgically implanted inside the eye and lasts for about 6-12 months)
- intravenous cidofovir (Vistide).
- fomivirsen (Vitrvavene), an antisense product designed to be injected directly into the eye;

Of these options, the ganciclovir implants (Vitrasert) generally provides the longest lasting protection from new or spreading CMV infection. Because it is implanted directly in the eye, however, it has no effect on the incidence of CMV elsewhere in the body.

The oral form of ganciclovir is sometimes used for maintenance therapy (after a course of intravenous therapy controls the spread of CMV) and for prevention of CMV disease. A number of other therapies for CMV retinitis in studies include:

- intravitreal cidofovir (a version of cidofovir injected directly into the eye);
- valganciclovir, which is a new version of oral ganciclovir that is far better absorbed into the bloodstream;
- Glaxo Wellcome 1263, an oral drug (taken by mouth, as a pill, rather than as an injection or infusion).

Of these, the two new oral drugs (valganciclovir and GW 1263) seem to offer the greatest promise of advances against the disease. Though

results are preliminary, there is already good indication that these new oral anti-CMV drugs may soon eliminate the need for routine intravenous therapy. They also appear to offer much greater promise as practical preventative agents.

Treatment of CMV retinitis usually involves two stages—induction therapy and maintenance therapy. Induction therapy is used to control the active spread of CMV and usually requires higher and/or more frequent dosing than what is required after the disease is initially brought under control. Once the spread of CMV is controlled, then a lower and/or less frequent dose is used to prevent CMV from reactivating. Previously, induction therapy was started for two weeks before going on maintenance therapy however, most CMV specialists now feel that it is essential to control the CMV before starting maintenance therapy. This might mean staying on induction therapy for more than two weeks.

Intravenous Ganciclovir (Cytovene) and Foscarnet (Foscavir)

Ganciclovir and foscarnet are administered through an intravenous (directly into the vein) central line (catheter), which has to be surgically implanted. Both drugs are systemic (throughout the body) and thus can prevent CMV from spreading throughout the body. At present intravenous ganciclovir is preferred over foscarnet as first-line therapy for CMV as it generally has fewer side effects and is better tolerated. One study actually demonstrated that foscarnet showed a significant survival benefit over ganciclovir (12.6 months compared to 8.5 months) in people with CMV retinitis, although this may be due to foscarnet's own possible anti-HIV activity. However, neither visual function nor CMV progression time differed between the two groups, and foscarnet was associated with more toxic side effects. Subsequent studies have shown no difference in survival time between people receiving foscarnet or ganciclovir.

Induction therapy differs slightly between the two drugs. Ganciclovir is given intravenously (5mg/kg) twice daily for at least two weeks. Foscarnet is administered intravenously (usually 90mg/kg) twice daily for at least two weeks. Foscarnet administration must be monitored because of its high toxicity and accompanied by infusion of saline hydration to decrease the drug's side effects on the kidneys. Administration of foscarnet sometimes requires hospitalization for a few days so that a person can be carefully monitored for side effects. One possible advantage of foscarnet is that it appears to have some degree of direct action against HIV as well as CMV, and as such, it may add to the overall anti-HIV effects of therapy. This could be particularly advantageous for people who are having difficulty keeping their viral load under control with standard HIV antivirals. However, some researchers feel this advantage is counteracted by the complexity of using the drug as well as its side effects.

Following successful induction, maintenance therapy continues with the administration of the drug indefinitely at a lower dosage. Ganciclovir is usually given intravenously at a dose of 5–10mg/kg

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once a day while foscarnet is given intravenously at a dose of 90–120mg/kg per day during the maintenance phase.

Recent research concluded that a combination of ganciclovir and foscarnet significantly delayed progression of CMV retinitis compared to use of either alone. However, volunteers had a significantly more side effects and poorer quality of life due to the longer infusion times of the two drugs, and no survival benefit was associated with the combination therapy. It is likely that such combination intravenous therapy will remain appropriate only in those instances when other therapies have failed.

Both ganciclovir and foscarnet have activity against other herpes viruses, with foscarnet being commonly used to treat acyclovir-resistant herpes.

People with catheters should carefully inspect the site of catheter insertion each day, and report any evidence of irritation or infection, tenderness or fluid discharge immediately to the physician. Men who are on foscarnet should carefully dry the penis after urination to reduce the chance of ulceration associated with foscarnet usage. People receiving foscarnet should closely monitor for electrolyte and mineral imbalances. Additionally, people on foscarnet should monitor serum creatinine levels for signs of kidney toxicities and people with kidney impairment may require a lower dose of foscarnet.

Cidofovir (Vistide)

Cidofovir is also approved for the treatment of CMV retinitis. Cidofovir has the advantage over other intravenous drugs in that it is administered only once (5mg/kg) a week for induction therapy and once (5mg/kg) every two weeks for maintenance therapy and therefore does not require a surgically implanted catheter, avoiding possible bacterial infections. Cidofovir has shown activity in laboratory studies against CMV and other herpes viruses, including zoster, Epstein-Barr virus and human papilloma virus. It is also active against CMV that is resistant to either ganciclovir or foscarnet, but is unlikely to be active against CMV that is resistant to both of these drugs.

While no studies have compared cidofovir to other CMV therapies, such as ganciclovir or foscarnet, results from the studies that have been conducted are encouraging. Approval of cidofovir was based on two studies showing that immediate cidofovir therapy can delay CMV progression at higher dose.

Cidofovir has a narrow dose range in which it is effective but does not cause significant side effects. In some studies side effects included proteinuria (high protein in the urine), neutropenia (abnormally low neutrophil cell counts) and peripheral neuropathy (pain or tingling in the hands, feet and/or legs). The major side effect of cidofovir, if used improperly, is serious kidney toxicity. To reduce this risk, people are given intravenous saline solution and a drug called probenecid before cidofovir infusions. Additionally, cidofovir should not be used in people with serum creatinine levels of more than 1.5mg/dL (mil-

ligram per deciliter), creatinine clearance of 55mL/min or less, or a urine protein level of 100mg/dL or more, all of which indicate kidney toxicity levels. People with decreased kidney function should use a reduced dose of cidofovir (3mg/kg).

Oral Ganciclovir (Cytovene)

Oral ganciclovir is approved for maintenance treatment of CMV retinitis. Although only 6% of the drug is maintained in the bloodstream when taken orally, there is less risk of developing catheter-related sepsis since the oral drug requires no central catheter. The oral drug is slightly less effective than the intravenous drug in preventing relapse of CMV disease and causes no additional side-effects. Because the oral drug is not well absorbed, large amounts are required and blood levels of ganciclovir are much lower when the drug is taken orally compared to blood levels achieved when the intravenous form is used. As a result, oral ganciclovir is not recommended for induction treatment of CMV retinitis. There is some concern that using the oral drug, with its low availability in the body, may lead to more rapid development of ganciclovir resistance and possible cross-resistance with other anti-CMV drugs (making those drugs ineffective in treating CMV).

A new version of oral ganciclovir, which is commonly referred to as valganciclovir is better absorbed into the bloodstream and the ganciclovir level found in blood is similar to that of the intravenous formulation. Valganciclovir is likely to be used as both induction therapy (twice daily dosing) as well as maintenance therapy (once daily dosing) thereby eliminating the use of intravenous drugs (and catheters) when treating CMV disease.

Ocular Ganciclovir Implants (Vitrasert)

The ganciclovir implant, which is also approved for the treatment of CMV retinitis, involves inserting a pellet containing ganciclovir directly in the eye. This therapy has three advantages to intravenous CMV therapy: it provides highly localized therapy for CMV retinitis; eliminates the need for daily intravenous infusions and the permanent insertion of a catheter (with associated risk of bacterial infections); and reduces systemic (through out the body) toxicity. However, the implants will not provide protection against CMV spreading to the other eye or to other parts of the body. Additionally, in some studies, there have been a higher rate of retinal detachments among people receiving the implants compared to those receiving systemic therapy, such as intravenous ganciclovir or foscarnet.

A study conducted at the National Eye Institute (NEI) found that the ganciclovir implants significantly delay progression of retinitis (by 226 days) in people with previously untreated CMV retinitis. This demonstrated an advantage over deferred treatment as well as over intravenous administered drugs (47 and 53 days for intravenous ganciclovir and foscarnet). In the NEI study, there was a high incidence of people who developed CMV in the other eye (50% at six months) or outside the eye (31%). However, another study comparing intravenous ganciclovir and implants showed no significant dif-



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ference in either the development of extraocular (outside the eye) CMV disease or development of CMV retinitis in the other eye. There was no significant survival advantage with implant use, but there is little reason to expect that treating CMV retinitis should provide a survival benefit since the infection threatens sight, but not life.

These studies suggest that the use of the ocular implants greatly extends the durability of treatment, resisting further retinitis in the infected eye two to three times longer than currently available therapies. A recent study found the combination of ganciclovir implant and oral ganciclovir was able to significantly delay the progression of CMV retinitis as well as protect against CMV from spreading to other body parts.

The unquestioned advantage of the implants is the improvement in quality of life for the person diagnosed with CMV retinitis. Prior to the implants, such a diagnosis was grim, requiring the insertion of an infection-prone catheter, followed by daily intravenous infusions for life. The implant is a relatively simple, outpatient procedure that protects the infected person for up to twelve months without any other form of therapy. Simply eliminating the catheter and the risk of associated bacterial infections reduces the apparent gravity of a CMV diagnosis. However, some caution that implants can cause transient decreases in vision and increased risk of retinal detachment.

Fomivirsen (Vitravene, ISIS 2922)

ISIS Pharmaceuticals is developing an antisense drug that works by binding a portion of CMV RNA and preventing viral replication. Twenty-two people (28 eyes) with CMV retinitis who had failed all other anti-CMV therapies were given different doses of fomivirsen by direct injection into the eye once weekly for three weeks, followed thereafter by a maintenance dose every other week. The drug may cause eye inflammation, which can be treated by topical steroids, and increased risk of retinal detachment. Some people maintained retinal stability without disease progression for over 50 weeks. However, the results are not directly comparable to larger studies of other treatments, and it is too early to know how fomivirsen will fit into the larger picture of CMV treatment.

Systemic vs. Localized Therapy

One of the most pressing questions for the treatment of CMV retinitis is whether localized therapy (treating a specific site, like the eye) is sufficient or superior to systemic (whole body) therapy. All intravenous and oral drugs are considered systemic whereas the ganciclovir implant, intravitreal cidofovir and Fomivirsen are “local” therapies, only treating CMV in the eye. Since CMV disease can effect the entire body, many physicians believe that some form of systemic therapy is required. Others believe that only CMV retinitis warrants constant treatment and that outbreaks of CMV elsewhere in the body can be handled if and when they occur. The potential benefit of systemic therapy is that they will provide protection against CMV disease spreading into the other eye or into other parts of the body. However, this comes at a high cost, as all the intravenous drugs currently available can cause severe side effects

and drug interactions. Systemic ganciclovir suppresses the bone marrow, while foscarnet and cidofovir can be very hard on the kidneys. Large amounts of drug are required to make sure the drug crosses the blood/eye barrier to have an effect against CMV retinitis. Typically, excessive amounts of drug must be used systemically to reach adequate levels inside the eye. Both foscarnet and IV ganciclovir require infusions daily and the insertion of a permanent catheter into a major artery. Such catheters bring with them a high risk of bacterial infections, such as sepsis, which can be difficult to treat in immunosuppressed people. Foscarnet also requires long, slow infusion times. Intravenous cidofovir has some advantages in that it requires infusion only once every other week, thereby eliminating the need for a surgically implanted catheter.

The advantages of local therapy include a much improved quality of life and greatly reduced risk of side effects. Ocular (eye) implants of ganciclovir are inserted once every six to eight months. Intravitreal injections occur more frequently but are still less burdensome than daily infusions and the constant risks associated with catheters and systemic treatment. Both approaches also seem to suppress disease in the eye much longer than the standard intravenous ganciclovir or foscarnet treatments. The only real question about their use is the risk of CMV outbreaks elsewhere in the body. Studies have so far failed to clearly quantify this risk.

As more therapies become available for the treatment of CMV retinitis, it becomes more essential to weigh the risks and benefits of all the different options. Old, new and soon-to-be-approved treatment options differ in their usefulness for different CMV-related conditions. In addition, their impact on quality of life and in drug-related side effects differs greatly. It is possible that some approaches may prolong survival more so than others, but due to the difficulty of conducting the large trials needed in people with advanced disease—the only place where CMV is a major problem—this effect may never be clearly understood. Thus, each individual must face the prospect of choosing a therapy based on factors such as quality of life, risk of side effects, risk of wider spread of the infection and more or less frequent need for additional therapy. Though not clearly documented, it is possible that new, more powerful treatments for HIV disease may themselves improve the effect of treatment for CMV infections.

CMV Colitis

Induction therapy with intravenous ganciclovir for enteritis or colitis usually lasts a week longer than for CMV retinitis, but the doses are the same. Induction treatment may be extended until the infection clears. Foscarnet will be chosen if platelet counts fall below 20,000/ul, or if ganciclovir therapy doesn't work.

Because CMV-related colitis is difficult to diagnose, most CMV drug studies have focused on retinitis. Some small studies have included volunteers with colitis and encephalitis (inflammation of brain tissue). One small study showed survival benefit with a ganciclovir and foscarnet combination therapy. A 1988 trial also established the value

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of high dose foscarnet (200mg/kg once daily for three weeks) in treating CMV colitis. It also remains to be seen if oral ganciclovir will be more effective at combating CMV colitis than intravenous drugs.

Drug Interactions

Drug interactions need to be considered when formulating a treatment strategy against CMV. Ganciclovir and AZT can cause neutropenia, although it is reversible with small doses of G-CSF or GM-CSF. Absolute neutrophil counts (ANC) should be closely monitored when ganciclovir is used in combination with other bone marrow suppressive therapies. Ganciclovir and ddI and/or d4T may increase the risk of developing pancreatitis.

Foscarnet is highly toxic to the kidneys, and people on foscarnet should not take other drugs that affect the kidneys, such as amphotericin B, the aminoglycosides (like amikacin), intravenous pentamidine and certain anti-inflammatories. People should also be aware of the increased risk of peripheral neuropathy (pain or tingling in the feet, hands and/or legs) from the combination of foscarnet and ddI.

Cidofovir is administered with probenecid which prevents kidney toxicity. The combination of ganciclovir and probenecid slows down the elimination of ganciclovir and sometimes results in generalized seizures. Foscarnet elimination is also affected by probenecid, so combinations of cidofovir with other currently approved intravenous therapies are potentially dangerous. Also, probenecid may interact with other commonly used HIV medications. Drugs causing kidney toxicity (see foscarnet drug interactions) should not be used with cidofovir. People planning to use cidofovir should allow at least seven days to “wash out” such other agents before beginning cidofovir therapy. Particularly, previous use of foscarnet may increase the likelihood of kidney toxicity.

Drugs that are injected directly into the eye are unlikely to interact with other drugs that are administered intravenously or orally, but such potential interactions should not be immediately dismissed. For more on potential drug interactions, call the Project Inform National HIV/AIDS Treatment Hotline at 800-822-7422.

Where to Get It

Ganciclovir, foscarnet, cidofovir, and the ganciclovir implants are available by prescription. Most states also cover these drugs through their AIDS Drug Assistance Program (ADAP). For information on your state ADAP eligibility and to find out if these therapies are covered through your state’s ADAP formulary, contact your state department of public health. Information is also available through the AIDS Treatment Data Network at 1-800-734-7104. People who lack insurance, Medicaid, ADAP coverage or personal financial ability to purchase the drug can sometimes gain access to therapies through the manufacturers Patient Assistance Program. For info on patient Assistance Programs for: ganciclovir (oral/IV) call 1-800-285-4484, ganciclovir implants call 1-800-843-1137, foscarnet call 1-800-488-3247 and cidofovir call 1-800-445-3235.

Commentary

A growing number of researchers and physicians believe the most effective and least invasive way to treat CMV retinitis may be to use a localized therapy for the retinitis in combination with an oral therapy for protection throughout the rest of the body. Intravenous cidofovir may also play an important role in this regard due to its infrequent dosing). This approach combines the high effectiveness and good quality of life associated with local therapy along with reasonable protection against CMV outbreaks elsewhere in the body. Some studies are already underway to determine if this is the overall best way of treating CMV retinitis. Even this strategy, however, may be changed if the initial promise of new oral drugs like valganciclovir is sustained. This could shift the burden of therapy almost entirely to oral medications. However, FDA approval of all new drugs for CMV is hampered by the low level of incidence of CMV infection in the era of HAART. The success of HAART in preventing CMV infections has made it extremely difficult to recruit enough people with new CMV to complete the required clinical trials.

There is a growing number of preliminary reports of people who have stopped CMV maintenance therapy because of sustained CD4+ cell count increases realized as a result of triple-drug combination of anti-HIV therapy including a potent protease inhibitor, without immediately relapse of CMV disease. However, it is still not known how long this will last, how soon after initiation of HAART it can be done, or whether everybody who have CD4+ cell count increases can stop their CMV maintenance therapy. Most researchers agree that there is likely to be much individual variation in these regards, probably based on the degree of immune function which was lost prior to initiating the triple-drug anti-HIV regimen. Many researchers believe that the specific types of CD4+ cells, which provide protection against opportunistic infections, may be lost due to immune deterioration and these cells do not necessarily return, at least in the short-term, when CD4+ cell counts increase as a result of triple-drug therapy. The longer term picture, however is less clear, with some researchers reporting successful return of many cells types previously thought to be lost.

New information on resistance to CMV therapies indicate that people resistant to ganciclovir are more at risk of developing resistance to foscarnet. If people are resistant to both ganciclovir and foscarnet, then they are at greater risk of developing resistance to cidofovir.

People with sight-threatening CMV retinitis should consider aggressive therapy such as a ganciclovir implant in addition to systemic intravenous therapy. People without sight-threatening CMV retinitis may be able to use therapies that allow for a better quality of life such as initial therapy with intravenous drugs and subsequent maintenance with oral or local therapy. While issues of resistance make the decision making process more complex, people should discuss these issues with their physicians to determine the most suitable course of therapy.



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THERAPY	ADVANTAGES	DISADVANTAGES
<i>IV ganciclovir (systemic)</i> [Cytovene]	<i>Physicians have the most experience with this drug; should prevent CMV from spreading elsewhere</i>	<i>Immunosuppressive and can cause many possible drug interactions; poor quality of life; surgically implanted catheter for daily infusions; risk of bacterial infections</i>
<i>IV foscarnet (systemic)</i> [Foscavir]	<i>Physicians have experience using this drug; should prevent CMV from spreading elsewhere</i>	<i>Requires careful monitoring due to side effects; poor quality of life; requires surgically implanted catheter with risk of bacterial infection; may have overlapping toxicity with cidofovir</i>
<i>Oral ganciclovir (systemic)</i> [Cytovene]	<i>Should prevent CMV from spreading elsewhere; improved quality of life</i>	<i>Requires large amount of drug; may be less effective; may contribute to more rapid development of resistance</i>
<i>IV cidofovir (systemic)</i> [Vistide]	<i>Should prevent CMV from spreading elsewhere; somewhat improved quality of life</i>	<i>Must be taken with probenecid to minimize side effects; possibility of drug interactions between probenecid and commonly used HIV medications; may have overlapping toxicity with foscarnet</i>
<i>Ganciclovir implants (localized)</i> [Vitrasert]	<i>Significantly increases time before relapse; improved quality of life; no risk of systemic side effects; no need for catheters and risk of bacterial infections</i>	<i>Will not prevent CMV from spreading elsewhere; fewer physicians have experience with this device; may cause an increased risk of retinal detachment</i>
<i>Fomivirsen - (localized)</i> [Vitravene]	<i>In laboratory tests it is active against ganciclovir and foscarnet-resistant CMV</i>	<i>Requires frequent direct injection into the eye; may cause an increased risk of retinal detachments</i>
<i>Intravitreal cidofovir (localized)</i>	<i>Infrequent direct injection into the eye; somewhat improved quality of life</i>	<i>Will not prevent CMV from spreading elsewhere; optimal frequency and dose of injections not yet known; high doses may lead to irreversible toxicity; may cause an increased risk of retinal detachment</i>
<i>Valganciclovir (oral ganciclovir pro-drug)</i>	<i>Simple to use, possibly equal or better in effectiveness than IV GCV; systemic coverage; probably useful in PX, RX, and MX</i>	<i>Systemic side effects likely</i>

The Bottom Line

Prevention:

- People with a sustained CD4+ cell count of less than 50, who have had a prior opportunistic infection, are most at risk for developing CMV disease.
- People with detectable CMV levels or are either antigen or culture positive for CMV are also at higher risk for developing CMV disease.
- There remains controversy over whether people should start preventative therapy against CMV with the current version of oral ganciclovir.

Treatment:

- There is no standard of care for the treatment of CMV disease. Several drugs are approved for the treatment of CMV (see table below for advantages and disadvantages for each therapy).
- Advantages of systemic (e.g. intravenous) anti-CMV therapies are that they may prevent CMV disease throughout the body. Disadvantages of these therapies is that they have more side effects than local (treating only the site of disease, like the eye) and impact quality of life (some require a surgically implanted catheter).
- Advantages of local (i.e. treating only the problem site, like the eye in the case of CMV-retinitis) are that they have far fewer side

effects compared to systemic therapy, thus greatly enhancing quality of life issues. Disadvantages of local therapy are that they do not prevent the spread of CMV disease into other parts of the body, and particularly do not prevent the spread of CMV into the unaffected eye.

Maintenance Therapy:

- There is no standard of care for the maintenance therapy of CMV disease. Generally, maintenance therapy is only started after the active CMV disease is controlled.
- Maintenance therapy should be continued indefinitely to prevent the infection from returning. In most cases, the infection will likely return if maintenance therapy is discontinued.
- It is currently not known if CMV maintenance therapy can be stopped if an individual on an aggressive triple-drug anti-HIV regimen, including a potent protease inhibitor, realizes substantial CD4+ cell count increases. This issue is currently under study. However, it is probably safe to assume that it would be very unwise to stop CMV maintenance therapy unless CD4+ cell increases as a response to aggressive anti-HIV therapy were sustained for a substantial period of time (6 months to 1 year) and HIV RNA levels remained very low, below the limit of detection of current tests.

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Cytomegalovirus Addenda Sheet



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reprinted from
PI Perspective #25, September 1998

In a study designed to examine cytomegalovirus (CMV)-specific immune responses in people stopping CMV retinitis maintenance therapy, it was found that 9/13 people developed vitritis (an inflammation in the eye) in the same eye as that of the retinitis. The vitritis was associated with decreased vision and led to blindness in some people. In general, people developed vitritis about three months after stopping CMV maintenance therapy and there was no evidence of re-emergence of the retinitis. Interestingly, people who had higher CD4+ cell count increases and stronger immune responses specific to cytomegalovirus were more likely to develop vitritis. The researchers believe that ironically people with stronger immune systems are still responding to residual cytomegalovirus in the eye and thus are experiencing this inflammatory response. If the inflammation is because of residual CMV, it may be possible to minimize the risk of vitritis by continuing on CMV maintenance therapy for a longer period of time. For those people who do decide to stop CMV maintenance therapy, it is advisable to be routinely monitored by an eye specialist (ophthalmologist). One caveat to these results is that the study was conducted at the University of California, San Diego where they routinely use intraocular injections (injection directly into the eye) of cidofovir (Vistide) to treat people with CMV retinitis. This is not the approved route of administration for this drug. Additionally, there have been anecdotal reports of vitritis in people treated with intravenous (injections into the veins) cidofovir while on HAART.

Advances in CMV Management: Formivirsen (Vitravene) Approved

reprinted from
PI Perspective #26, December 1998

The recommended dose is 330µg on days 1 and 15 during the initial phase of treatment (when CMV is still spreading). It is then given once monthly during the maintenance phase (when CMV is not actively spreading but requires therapy to prevent it from reactivating). Studies show fomivirsen works equally well in people with newly diagnosed CMV retinitis as in those receiving other CMV therapies.

Since fomivirsen blocks CMV from replicating through a different mechanism than that of other approved CMV retinitis therapies, people who have developed resistance to other therapies may still benefit from this drug. Because fomivirsen is administered directly into the eye, it does not cause any systemic (throughout the body) side effects. However, in some studies, some people had retinal detachments. In one study that employed a higher dose in people with newly diagnosed CMV retinitis, some developed retinal stippling (spots in the retina) which resulted in some loss of peripheral vision. The fact that it works only locally in the eye also prevents the drug from suppressing CMV infections elsewhere in the body, a limitation not shared by most other treatments for CMV retinitis.

Though there have been no results directly comparing fomivirsen with other approved therapies, the results from studies so far suggest it is comparable in effectiveness to intravenous ganciclovir (Cytovene),

The Food and Drug Administration recently approved a new treatment for cytomegalovirus (CMV) retinitis, an opportunistic infection affecting people with advanced HIV disease. Left untreated, CMV can lead to blindness. Fomivirsen (Vitravene, formerly ISIS 2922) is given by injection directly into the eye by an ophthalmologist (eye specialist) every two or four weeks.

foscarnet (Foscavir) and cidofovir (Vistide) in suppressing and preventing the recurrence of active CMV retinitis. However, the ganciclovir implant (Vitrasert), which is surgically implanted into the eye and slowly releases ganciclovir, has demonstrated much longer lasting anti-CMV retinitis effects. Nonetheless, fomivirsen is a welcome addition to the arsenal of anti-CMV therapies, especially because of its ability to work after resistance develops to other CMV therapies.

500mg Ganciclovir Capsule

A new 500mg capsule of ganciclovir (Cytovene) is now available for use in the prevention and maintenance treatment of CMV disease. Previously, oral ganciclovir was only available in 250mg capsules, and when used for prevention or maintenance of CMV disease, required twelve capsules a day (1,000mg three times a day). This new 500mg capsule will reduce by half the number of pills needed daily.

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Cytomegalovirus Addenda Sheet

Oral ganciclovir is poorly absorbed into the body and therefore is considered second-line therapy for the maintenance of CMV disease. However, because all other systemic therapies for CMV are administered intravenously (directly into the vein), many people opt for oral ganciclovir because it does not require a surgically implanted catheter, which is accompanied by a risk of serious bacterial infections.

Oral ganciclovir is also sometimes used for prevention of CMV disease in people with severely compromised immune systems, but this use of

the drug remains controversial because of conflicting study results. More importantly, the success of HAART today in partially restoring immune function has diminished the need for preventive use.

A new formulation of oral ganciclovir, sometimes known as pro-ganciclovir or valganciclovir, is currently in studies. This new formulation is so much better absorbed by the body that the sponsor hopes it may eventually eliminate the need for intravenous therapy altogether.

Cytomegalovirus

reprinted from
PI Perspective #27, April 1999

Cytomegalovirus (CMV) is a potentially life-threatening virus and is the leading cause of blindness in people with HIV disease. Recent evidence suggests that the incidence of CMV is down. A number of studies are looking at the feasibility of stopping therapy aimed at preventing recurrence of CMV disease (or maintenance therapy). Results so far suggest the need for caution when one thinks about stopping maintenance therapy. They underline the continued importance of CD4+ cell counts as the primary measure for determining one's immediate risk of developing CMV.

One study reported on 17 people who stopped their CMV maintenance therapy after getting an increase in CD4+ cell counts from HAART. All of the participants had CD4+ cell counts over 70 and had healed CMV retinitis, an inflammation of the eye that can cause blindness if left untreated. Despite continuing their HAART regimen, five of the seventeen participants had their CMV retinitis reactivated after being off maintenance therapy for 6-28 months. All volunteers who had CMV reactivation had seen their CD4+ cell counts return to below 50 and typically had higher HIV levels compared to people who did not have reactivation. Also, five of the six people with CMV reactivation had very low levels of the immune system marker that has

the ability to combat CMV (called CMV-specific lymphoproliferative responses). No participant who maintained CD4+ cell counts above 100 had CMV reactivation. This study suggests it may be wise to wait until CD4+ cell counts go above 100 for several months before discontinuing CMV maintenance therapy. Also, people who have a subsequent decline in CD4+ cell counts to below 75 may want to reconsider starting CMV maintenance therapy before CMV reactivation recurs. In many ways, these findings reflect the general guidelines employed for CMV before the use of highly potent antiviral regimens. Earlier guidelines typically suggested taking CMV prevent medications when the CD4+ count fell below 75.

A New Acronym, a New Threat: IRU

reprinted from
PI Perspective #28, September 1999

Eye doctors (ophthalmologists) have recently observed the appearance of eye inflammation in people who have experienced remission of cytomegalovirus (CMV) retinitis in response to highly active antiretroviral therapy (HAART). This eye inflammation is currently called *Immune Recovery Uveitis* (IRU). Uveitis is an inflammation inside the eye which can result in significant vision loss. IRU has only been observed in people who started HAART and had a significant increase in CD4+ cell counts and who have stopped their anti-CMV therapies. Additionally, IRU only occurs in eyes that were previously diagnosed with CMV retinitis.

One hypothesis for IRU is that there may still be low level CMV replication in the eye. The newly invigorated immune response may be attacking the CMV and causing inflammation. There are several unknowns at this point. It is not known if people who have the ganciclovir implants (Vitraser) to treat CMV are as likely to develop IRU because the implants are better able to control CMV replication. It is also not known if IRU will improve if someone resumes CMV therapies.

Ophthalmologists have tried a few different therapies to treat IRU with limited success, including systemic prednisone, periocular

(around the eye) injections of prednisone and methylprednisolone (Depo-Medrol). In most instances, when these medications were stopped, the IRU returned.

A large observational study has started at the Studies of Ocular Complications from AIDS (SOCA) sites and it is hoped that this study will be able to assess the incidence and prevalence of IRU, the cause of IRU and strategies to treat it. In the meantime, people who previously had CMV retinitis should consider the risk of IRU when thinking about stopping CMV maintenance therapy.

Cytomegalovirus Addenda Sheet



Advances in Treating CMV

reprinted from
PI Perspective #30, August 2000

Long-awaited results from a study of treating CMV (cytomegalovirus) retinitis show that a new formulation of oral (by mouth) ganciclovir, known as valganciclovir, is as effective as the intravenous (IV, injection into the vein) version of the drug. This is the first time that an oral drug for treating CMV has been shown to be as effective as the IV version.

The use of valganciclovir results in similar drug levels in blood as those produced by the IV form. This is a major improvement over the currently approved oral form of ganciclovir (Cytovene), which is hampered by poor absorption into the bloodstream and consequently weak control of CMV. The standard version of oral ganciclovir is only approved for maintenance therapy (to prevent CMV from recurring in people who have already been treated for the disease) and for preventing initial CMV disease (though the data for prevention use are weak and conflicting). It is not approved for treating the active disease.

Study Results

The study included 160 people with active CMV disease and CD4+ cell counts averaging around 25. About 25% of the volunteers were not on highly active anti-HIV therapy when they started. Participants received either 900mg of valganciclovir twice a day for three weeks followed by one week of 900mg daily or 5mg/kg of IV ganciclovir twice a day for three weeks followed by one week of 5mg/kg daily.

There was no difference in rates of CMV disease progression between the two groups at the end of four weeks. About 10% in each group continued to have progressive CMV disease, and about 65% in each group responded well in controlling the virus. There are no data yet to show whether valganciclovir is equivalent to the IV formulation in the time to relapse (when CMV recurs).

Future Study

A large study is planned to look at the effectiveness of preventive CMV treatment with valganciclovir. It will study the drug's use in people without CMV disease who have measurable CMV levels in their blood (called CMV PCR positive). Several studies have shown that CMV PCR positive people are more likely to develop CMV disease than CMV PCR negative people.

If this strategy works, it will mean that only people at risk for developing CMV disease would need to use preventive therapy. This is unlike the current standard in which people consider CMV prevention therapy based solely on their CD4+ cell counts. This will reduce the cost of HIV care as well as spare people from risking the side effects of potentially unnecessary therapy.

The major points from *Treating CMV*

- A new oral drug, valganciclovir shows effectiveness in treating CMV.
- This is the first oral drug shown to be as effective as standard IV therapy for treating this condition.
- Future studies will examine how useful this drug is in preventing CMV.

Other PI Publications

Project Inform (PI) has developed more than a hundred publications including Fact Sheets, Discussion Papers, Charts and the PI Perspective (the journal of Project Inform) designed to make information about medical therapies, research advances and living with HIV disease approachable. All of these publications are available through the Project Inform's National HIV/AIDS Treatment Hotline.

Project Inform has information on many topics including:

Anti-HIV Therapy Strategies
Building a Doctor Patient Relationship
Day One
Drug Interactions
Drug Side Effects
OI Chart
Maintaining Adherence to HAART
Nutrition and Weight Maintenance
and many more!

This list is updated as new information develops, but it does not include all the materials available. Please call the Project Inform Hotline, or check out the website below for even more PI Publication titles.



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