Cytomegalovirus retinopathy: current concepts and therapeutic options

Retinopatia por citomegalovírus: conceitos atuais e opções terapêuticas

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Cytomegalovirus (CMV) retinopathy is the most common infection of the eye in patients with acquired imunodeficiency syndrome (AIDS) and is a major cause of AIDS-related morbidity. As attention has become focused on quality of life issues in the fight against AIDS, CMV retinopathy has become a subject of intense study. Great progress has been made in the treatment of CMV retinopathy over the past decade; with the availability of ganciclovir and foscarnet, it is rare for patients to die blind. With experience, though, have come many controversies regarding the best management of CMV retinopathy. They range from a variety of issues dealing with early and accurate diagnosis of patients needing treatment, to the best drugs and treatment regimens, to the treatment of complications. This review will cover current treatment options for CMV retinopathy and concepts about the disease that help in making management decisions. It will focus on several controversies including deferral of treatment at diagnosis; the benefits of ganciclovir versus foscarnet; and the management of late disease reactivation and progression.

CMV retinopathy is a necrotizing infection that destroys all layers of the retina. It is associated with surprisingly little tissue inflammation. The appropriate management of CMV retinopathy of course depends on accurate diagnosis, which is based on clinical findings. There are no blood tests, for example, that will confirm an ocular infection. At least half of the world's adult population is infected with CMV, and probably 95% of AIDS patients have positive CMV sorologies, whether or not they have CMV retinopathy. It is therefore important to recognize the spectrum of its clinical manifestations.

At one end of the spectrum are the "fulminant/edematous" type of lesions. These have the "classic" appearance of CMV retinopathy, characterized by dense opacification throughout the lesion. They are usually located adjacent to retinal vessels, and have variable degrees of dense hemorrhage and retinal vasculitis.

At the other end of the spectrum are the "indolent/granular" type of lesions, characterized by less dense opacification, usually with little hemorrhage. They have an atrophic center, suggesting that the lesions are expanding so slowly that the body has time to completely clear the necrotic debris from this area.

Here are two more lesions of the indolent/granular type. They almost appear to have been treated, although in these cases they were not. These lesions are sometimes called "atypical retinitis", but ironically they are the most specific for CMV retinopathy; the very dry, granular border that is best seen in this type of lesion, coupled with the scant inflammatory reaction, occurs in no other disease.

About a dozen retinal or choroidal pathogens have been identified in patients with AIDS. Most are uncommon, and only a few can be confused with CMV retinopathy. Herpes sim-

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plex virus infections of the retina are extremely rare; only 2 or 3 presumed cases have been seen at UCLA in the past 10 years. There is no granularity to the deep retinal lesions of early infection.

The "progressive outer retinal necrosis syndrome" is a rapidly progressive necrotizing retinopathy that involves both the peripheral retina and macula, and has little-associated inflammation. It is caused by varicella-zoster virus (VZV) and is distinct from another VZV-related disorder, the acute retinal necrosis syndrome. Although uncommon, it is the second most frequent ocular infection that we see in AIDS patients. Several features distinguish it from CMV retinopathy: the homogeneous deep retinal opacification without granular borders; the early involvement of the fovea; and its very rapid course. Almost invariably these patients lose all vision, even with aggressive antiviral therapy. Most patients have been treated with intravenous acyclovir, but recently foscarnet has been used as an alternative therapy for this disorder.

The only other retinal infection that is seen with any frequency in AIDS patients is ocular toxoplasmosis; still it only accounts for about 1-3% of retinal infections. Typical features of the disease include densely-opaque, necrotizing retinitis that has a more "indurated" appearance than CMV retinopathy; no hemorrhage; and a prominent vitreous inflammatory reaction.

Syphilis is more likely to cause posterior segment disease in patients with AIDS. It can either result in deep subretinal plaque-like lesions or grainy retinitis. The latter form of disease might be confused with the indolent/granular form of CMV retinopathy if it was not for the prominent vitreous inflammatory reaction.

The most important clinical feature that helps to distinguish syphilis or ocular toxoplasmosis from CMV retinopathy is a prominent inflammatory reaction. You will never see a red eye, fibrin clots, or posterior synechiae in an AIDS patient with CMV retinopathy.

Recently intraocular lymphomas with retinal involvement have been described in patients with AIDS. In some cases, it can resemble CMV retinopathy.

Cotton-wool spots occur in at least two-thirds of patients with AIDS. They are usually easily distinguished from early foci of CMV retinopathy by their sharply demarcated borders, "squiggly" appearance, and superficial location. Occasionally, however, a large cotton-wool spot can be confused with an early focus of CMV retinopathy. Close follow-up, over a 2-week period with usually reveal whether lesions are cotton-wool spots; they resolve spontaneously, while CMV retinopathy will progress.

Choroidal diseases, such as choroidal pneumocystosis and *Mycobacterium avium* complex choroiditis, should not be confused with CMV retinopathy because of their multifocal appearance and location deep to the retina.

The epidemiology of CMV retinopathy has been studied. In preparing for clinical trials, we need information on prevalence, patients at risk, and survival. And of course this information is important for patients and their primary care providers.

The exact prevalence of CMV retinopathy in patients with AIDS is not known, but most investigators agree that 15-25% of patients will develop this infection at some point during the course of their disease. The development of CMV retinopathy in a previously healthy individual without other causes for immunosuppression is sufficient criteria for a diagnosis of AIDS. It is, however, usually a late manifestation of disease, occurring only in patients with the most severe degrees of immunosuppression; therefore, only about 2% of patients will have CMV retinopathy as their index diagnosis for AIDS. Based on prevalence, statistics, and incidence figures for the development of AIDS in HIV-infected individuals, the risk of an HIV-infected individual developing CMV retinopathy during the first 7 years after HIV infection has been calculated to be less than 1/2 of 1%; therefore large scale screening programs, which were initially advocated by some, would be of little value.

The median interval between a diagnosis of AIDS and the development of CMV retinopathy is approximately 9-10 months. Survival of patients with CMV retinopathy has been increasing over the years; still, patients have a median survival of only 8-12 months after development of CMV retinopathy.

Who is at greatest risk for development of CMV retinopathy? There is a negative correlation with CD4-positive lymphocyte counts. There is an increasing risk of CMV retinopathy as a patients's CD4 count falls during the course of their disease (Robert Murphy, M.D., Northwestern University, Chicago, ILL, personal communication). Nearly all patients with CMV retinopathy will have a CD4 count less than 50.

It has been a mystery why CMV retinopathy is so much more common among patients with AIDS than among other patients with systemic CMV infection and severe immunosuppression, such as solid organ transplant and bone-marrow transplant recipients, in whom the prevalence is only about 1%. It may be related to microvascular disease, CMV retinopathy frequently develops adjacent to retinal vessels, probably because the virus reaches the eye in infected leukocytes during CMV viremia. Also,

most, if not all, patients with HIV infection have a diffuse retinal microvasculopathy very similar to diabetic retinopathy, that results in the focal ischemia that causes cotton-wool spots and retinal hemorrhages. Ultrastructural studies show marked narrowing of capillary lumina.

Using the conjunctiva as a model of HIV-associated microvasculopathy, it has been shown that the severity of microvascular disease was correlated with fibrinogen levels and with increased red cell aggregation, as measured by the zeta sedimentation ratio. Both of these factors lead to sludging of blood flow. It is possible that the combination of capillary closure and decreased transit time through the retinal capillary network may place patients with AIDS at increased risk of developing a retinal infection during prolonged CMV viremia.

One of the oldest conroversies in the management of CMV retinopathy is whether treatment for small lesions outside the major vascular arcades can be deferred for 2 weeks, a month, or even longer, without adversely affecting the patient's ultimate visual outcome. Decisions about this issue require an understanding of the natural history of CMV retinopathy.

CMV retinopathy usually starts as a single focus of disease, which then expands to destroy the entire retina over a several-months period. It is probably difficult to establish the first infection, since patients usually have only 1 or 2 foci at presentation. It is uncommon for a new lesion to develop even if lesions are progressing.

It is also unusual for a lesion to develop in the fovea. As lesions spread, they tend to progress circumferentially around the fovea, rather than straight toward it. These observations have led to the concept that CMV retinopathy is relatively "foveal-sparing". Thus, an untreated lesion may pose little threat to vision for some time after diagnosis.

The kinetics of disease progression have been studied in untreated patients. In nearly all patients studied, the rates of progression were different in various directions. Very characteristic, however, was the fact that anterior progression towards the ora serrata is faster than posterior progression towards the fovea. Although progression rates vary widely, the untreated disease approaches the fovea at approximately 24 microns per day. Also, fulminant/edematous lesions probably progress faster than indolent/granular lesions.

There are many patients with peripheral indolent/granular disease who have elected not to undergo treatment immediately. When treatment is finally started after a few weeks in such cases, vision can remain unchanged, there are typically no new lesions, and patients subsequently do very well with therapy.

With currently available drugs, there are several reasons why deferral of treatment would be desirable. Both ganciclovir and foscarnet are available only as an intravenous drug, and treatment is very expensive; in Los Angeles, a year of therapy with ganciclovir can cost $ 30,000, and a year of therapy with foscarnet can cost over $ 100,000 when one considers both the cost of the drug and the equipment and medical care associated with its administration. Deferral of treatment will avoid this initial expense and inconvenience.

Second, deferral of treatment will avoid drug toxicity. Both ganciclovir and foscarnet have severe side effects; ganciclovir is a bone marrow suppressant and foscarnet can have severe renal toxicity.

Also, deferral of treatment will avoid catheter sepsis, which has been reported to occur at a rate of 2/1000 catheter-days.

Before the availability of foscarnet and newer antiretroviral drugs, a major consideration was that deferral of treatment allowed patients to continue using full-dose zidovudine, which could not always be used with ganciclovir because of competing toxicities.

There are, of course, arguments in favor of immediate treatment: It will reduce the risk of new lesions even further; it prevents the enlargement of lesions, which might reduce the risk of retinal detachments; and it presumably treats clinically-inapparent, non-ocular sites of CMV infection that might eventually be life-threatening. The issue of immediate versus deferred treatment has not yet been resolved. And, of course, as less toxic drug therapies are developed, the risk/benefit analysis will undoubtedly favor earlier treatment.

Specific terminology and concepts have been developed that facilitate standardized reporting of various multi-center studies of CMV retinopathy treatment. First, the location of lesions is described by zone. Lesions within zone 1 (within 1 disc diameter of the optic nerve head margin or within 2 disc diameters of the center of the fovea) are considered immediately vision-threatening, while lesions in zones 2 and 3 (the "peripheral retina") are not.

The concept of the lesion border is important. In many cases, there is a transition zone between normal and necrotic retina that is characterized clinically by multiple "white dots". The border of the lesion should encompass all white dots.

The assessment of disease outcome in clinical trials is based on the philosophy that treatment is given to prevent infection of additional normal tissue. Thus, progression is defined only by the development of new lesions or enlargement of pre-existing lesions, regardless of lesion appearance. Changes in retinal opacity is a poor

surrogate for progression, since lesions can continue to enlarge even with a decrease in opacity. Nevertheless, persistent border activity is a reasonably good predictor of eventual progression. Opacity is important only at the lesion border, which represents the area of active advancing infection. Opacity in more central areas of the lesion represents exudative material, necrotic debris, or possibly calcium. The degree of border opacification can very widely letween different patients, and we usually refer to lesions only as being either active or inactive.

When the AIDS epidemic began, there were no effective treatments for CMV retinopathy. In 1984, ganciclovir became available on compassionate use basis. It inactivates the virus but does not eliminate it from the eye. Therefore, patients are first given an induction course to inactivate the lesions, followed by life-long maintenance therapy to prevent disease reactivation. In 1991, a second drug, foscarnet, was also approved by the FDA for treatment of CMV retinopathy. It is used in the same manner. Both drugs are currently available only in an intravenous preparation and therefore patients must receive home infusions. Although treatment can inactivate lesions, there are a number of problems with their use. In addition to the problems already described, we now know that lesions will eventually reactivate and progress in most patients, if they survive long enough, even with maintenance therapy.

There have been a number of reports documenting virus resistance to ganciclovir or foscarnet. There is still poor correlation, however, between in vitro tests of drug resistance and clinical response to drug treatment.

The SOCA Foscarnet-Ganciclovir CMV Retinitis Trial, which was recently reported in the New England Journal of Medicine, was designed to compare the efficacy and safety of ganciclovir versus foscarnet, and to study the risks and benefits of immediate versus deferred treatment for small peripheral lesions. The study had a fairly complicated design based on lesion extent and location. One aspect of the study was the randomization of patients with small peripheral lesions in zones 2 or 3 to immediate versus deferred therapy until progression was noted. Because the issue of treatment deferral is controversial, patients were actually allowed to state their preference between immediate treatment, randomization, or deferral. Analysis of this part of the trial is still incomplete.

The New England Journal of Medicine publication resulted from the fact that the treatment protocol was stopped prematurely when it was discovered that patients receiving foscarnet survived longer than patients receiving ganciclovir; the article discusses only that aspect of the study. Patients treated with ganciclovir survived a median of 8.5 months while patients receiving foscarnet survived a median of 12.6 months, which was a highly significant difference. Because of its renal toxicity, foscarnet had a survival benefit only for those patients with normal creatinine clearance. The cause of the differential survival could not be determined. It might be related to the drugs themselves since foscarnet has some antiretroviral activity. It might also be related, in part, to other uncontrolled variables such as the use of other antiretroviral drugs. Patients on foscarnet can receive full-dose zidovudine, which is known to prolong life, while patients on ganciclovir sometimes cannot, since they are both bone marrow suppressants.

There was no difference between the two drugs for major ophthalmic end-points, such as final visual acuity or median time to reactivation and progression, which was slightly under 60 days for both drugs. We still have not analyzed our data for more subtle differences between the drugs, such as the extent of progression when it does occur.

The drugs are not equal in their associated non-ocular morbidity, however. There was a much higher ''switch rate'' in patients on foscarnet meaning that they could not tolerate treatment and had to be changed to ganciclovir. These increased switches for patients on foscarnet were most commonly related to its toxicity.

The questions of which drug is truly ''better'' therapy remains to be determined. Since there are no obvious differences in the ability of these two drugs to control retinopathy, the patient's primary care provider should be involved in choosing which drug to use, based on non-ophthalmic factors such as side effects, drug tolerance, and survival issues. Interestingly, when the SOCA treatment protocol was terminated, only 20% of patients and their primary care providers elected to switch from ganciclovir to foscarnet, despite its reported survival benefit.

The SOCA studies concentrated on the management of newly diagnosed CMV retinopathy, for which we expect complete resolution of disease activity after a 2 week course of induction therapy. They did not specifically address the question of ''breakthrough'' or reactivation and spread of disease during maintenance therapy.

Reactivation is now believed to occur in all patients, if they live long enough. The cause for this phenomenon is uncertain; although viral resistance has been reported in some cases, continued waning of the host's own immune defenses is probably the major factor responsible for poor control in most cases.

In many patients, reactivated disease can again be brought under con-

trol through reinduction, which is the administration of another 2-week course of high-dose therapy. This observation suggests that current maintenance drug levels are inadequate for control of disease; it is difficult, though, to continue higher doses of maintenance therapy because of the drugs' toxicities.

Another interesting finding in the SOCA trial was that reinductions occur at decreasing frequencies, indicating that CMV retinopathy is harder and harder to keep in control as time goes on. Eventually, it may become impossible to inactivate lesions, and the best that can be hoped for is slowed progression. Despite agressive therapy, some patients with very long survival can eventually have total retinal destruction through slow spread of disease.

There are some patients who seem to have inactive lesions during maintenance therapy, but continue to have progressive destruction of the peripheral retina. It may be difficult to see any obvious border opacification, although presumably the lesions continue to have very low-grade viral activity. This phenomenon has been called "creeping scars" by some investigators.

The management of late progressions is currently the most pressing issue surrounding CMV retinopathy, and will be the problem addressed in the second large trial at SOCA Centers. In the CMV Retinitis Relapse Trial patients with disease reactivation will be randomized to one of several different maintenance therapies using various doses of foscarnet or ganciclovir. They include: switching from ganciclovir to foscarnet or vice versa when reactivation occurs; the combined use of ganciclovir and foscarnet, based on in vitro evidence that ganciclovir and foscarnet are synergistic; and the continued administration of induction level ganciclovir with the concurrent administration of leukocyte growth factors, such as granulocyte-monocyte colony stimulating factor (GM-CSF) or granulocyte colony stimulating factor (G-CSF), which will prevent drug-induced neutropenia.

Because of drug toxicity, local therapies for CMV retinopathy have been investigated. They include intravitreal ganciclovir, a recent report of implantable devices with slow release ganciclovir, and the possibility of iontophoresis of foscarnet.

I am frequently asked about intravitreal injections of ganciclovir. This treatment can be used successfully to control CMV retinopathy, but has many disadvantages including the complications of the injections themselves, such as endophthalmitis; the logistical difficulties of giving patients intraocular injections on a once or twice weekly basis indefinitely; the fact that it treats only ocular disease, despite the fact that patients with CMV retinopathy invariably have tissue-invasive CMV infections of other organs at the same time; and indications that ganciclovir injected intravitreally may have greater retinal toxicity than heretofore believed.

Several years ago intravitreal ganciclovir was the only alternative to systemic ganciclovir. It was indicated for patients who developed neutropenia; for patients who had progression of lesions despite continued maintenance therapy; for those who wished to take concurrent zidovudine therapy for its survival advantage; and as a means of reducing catheter-related sepsis. There are now, or may soon be, more appropriate alternatives for each of these indications. Patients with neutropenia can be switched to foscarnet or given leukocyte growth factors. We believe that simple reinduction therapy alone is just as effective as supplemental intravitreal ganciclovir for patients with progression. Zidovudine can be taken in full doses with foscarnet and newer antiretroviral drugs such as didanosine do not have competing toxicities with ganciclovir. And finally, oral formulations of these drugs that are in development will reduce the risks of catheter sepsis.

Another management problem that usually occurs late in the course of CMV retinopathy is retinal detachment. There is an increased risk of retinal detachments in patients with lesions extending to the ora serrata and when greater than 50% of the peripheral retina is infected. They are becoming increasingly common as patient survival increases; 50% or more of patients can be expected to develop retinal detachments if they survive long enough. More controversial is the relationship between disease activity and retinal detachments and a possible relationship between retinal detachments and antiviral drug treatment.

These detachments can be successfully repaired with silicone oil tampanode, but there are several problems associated with this therapy, including induced hyperopia that requires contact lens rehabilitation; cataract formation; and in many cases, final visual results have been disappointing, even if the macula remains attached and noninfected.

Oral ganciclovir is currently being studied in clinical trials. Because of its low bioavailability, it is used only as a maintenance agent after successful intravenous induction. It successful, it will simplify the long-term management of CMV retinopathy, but patients will still need periodic intravenous reinductions.

There are many new drugs and therapies in development for CMV retinopathy. New drugs include cyclobutol-G and HPMPC, but they are not yet ready for clinical testing. Adjunctive therapies have also been investigated. Leukocyte growth factors, in-

cluding G-CSF and GM-CSF have been used to maintain adequate neutrophil levels despite the bone marrow toxicity of ganciclovir. There has been considerable interest in the use of CMV hyperimmune globulin, bu it has not yet been shown to be useful in the management of CMV retinopathy, when used as an adjunctive therapy to ganciclovir.

Prophylactic therapy will be attempted to prevent disease development altogether. Two drugs are being considered as prophylactic agents. The first is oral ganciclovir and the other, BW 256U87, is an oral prodrug of acyclovir from Burroughs Wellcome Company. Although acyclovir is not a good anti-CMV agent, the very high levels of acyclovir achieved with this new drug may be adequate to prevent development of new infections. Before widespread prophylaxis in instituted, though, additional information is needed regarding risk factors, so that we can identify that sub-population who would benefit most from these drugs.

In conclusion, the management of CMV retinopathy remains a challenging problem. We need to determine the most effective use of current drugs, while searching for new therapies that are simpler, more cost-effective, and provide the best quality of life for patients with this disease.