Cytomegalovirus retinitis in Cape Town, South Africa: Clinical management and outcomes

S R J Lapere, MB ChB, FCOphth (SA), MMed (Ophth); **J C Rice**, MB BCh, FCOphth (SA), MRC Ophth, MPH (Clinical Research)

Department of Ophthalmology, Groote Schuur Hospital, Cape Town, South Africa

Corresponding author: *S R J Lapere (steven.lapere@gmail.com)*

Background. Cytomegalovirus (CMV) retinitis is a vision-threatening opportunistic infection that occurs mainly in immunocompromised individuals. Limited data on treatment protocols and management outcomes are available in South Africa (SA).
Objectives. To review the clinical presentation, management and outcomes of patients who were diagnosed and treated for CMV retinitis at Groote Schuur Hospital, Cape Town, SA, over a 10-year period, and to compare treatment protocols of 13 public hospitals in SA that treat patients for CMV retinitis.
Methods. A retrospective case review was performed of all patients treated for CMV retinitis at Groote Schuur Hospital between 2003 and 2013. In addition, a questionnaire was sent to 13 public hospitals in SA that treat patients with CMV retinitis.
Results. A total of 141 eyes in 91 patients were polymerase chain reaction-positive for CMV. Of these patients, 98.6% were HIV-positive and 72.5% were on highly active antiretroviral therapy (HAART) at the time of presentation. Patients who were on HAART at presentation had better mean final visual acuity (VA) than those who were not on HAART ($p<0.001$). There was a significant association between the number of retinal quadrants involved and final visual outcome ($p=0.009$). Macular (central vision) involvement had a significant adverse effect on visual outcome compared with cases in which the macula was uninvolved ($p=0.005$).
Conclusions. Independent risk factors that predict final visual outcome include presenting VA, number of retinal quadrants involved, macular involvement and being on HAART at presentation. The diagnosis and management of CMV retinitis differ among treatment centres in SA.

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Cytomegalovirus (CMV) is a ubiquitous member of the family Herpesviridae. It persists in the body like other herpesviruses, resulting in latency. It is continually suppressed by cell-mediated immunity, so infection is usually asymptomatic in immunocompetent hosts. CMV retinitis is a relentless vision-threatening infection that can cause irreversible vision loss within weeks to months.[1] Most cases are diagnosed clinically, as it has a characteristic fundoscopic appearance. The classic appearance is a 'bushfire-like' extension along the course of the retinal vascular arcades that may involve the optic nerve head (Fig. 1).

CMV retinitis is the most common cause of vision loss in patients with AIDS.[2] It is an opportunistic infection and a late manifestation of HIV infection, usually associated with CD4 counts of <50 cells/μL.[3] Before the advent of highly active antiretiroviral therapy (HAART), treatment of CMV retinitis was lifelong and mortality rates due to HIV were high. With the advent of HAART, there has been a 75% reduction in the number of new cases of CMV retinitis.[4]

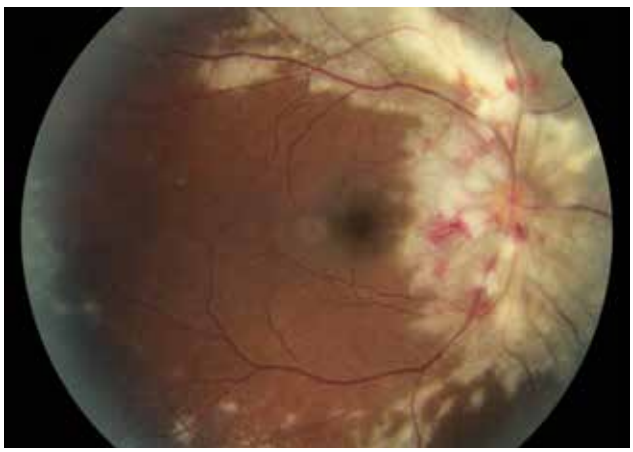

Fig. 1. Cytomegalovirus infection with typical 'bushfire-like' extension along the vascular arcades with retinal necrosis.

The principles of treatment of CMV retinitis are to improve the patient's immune function and to use specific anti-CMV agents to inhibit viral replication. Many studies have investigated the effect of HAART on CMV retinitis.[5] The incidence and recurrence rates have been shown to decrease as a result of the restored immunity that HAART provides.[6] In addition, anti-CMV treatment can usually be discontinued once immune reconstitution has occurred.

CMV targeted treatment options include intravenous, oral and intravitreal antivirals. Intravitreal ganciclovir has been the mainstay of treatment for CMV retinits in South Africa (SA) and has been shown to have a better pharmacokinetic profile than intravitreal foscarnet,[7] although recent evidence[8] suggests that systemic treatment should be considered. Systemic treatment has a higher risk of side-effects than ocular treatment and has significant cost and resource implications. Ganciclovir causes haematological abnormalities (anaemia, neutropenia and thrombocytopenia) and may result in long-term reproductive complications.[9] Foscarnet is highly nephrotoxic and must be administered with caution to patients with renal disease. Oral valganciclovir has a bioavailability of 60% and can be used as an adjunct for both induction and maintenance therapy. At the time of this study, intravitreal ganciclovir alone, without systemic anti-CMV treatment, was used to treat all patients with CMV retinitis. The decision when to stop anti-CMV therapy depends upon many factors, including rising CD4 counts, decreasing systemic HIV viral load, duration of HAART and inactivity of CMV

lesions.[4] The US Public Health Service provided guidelines in 1999[10] suggesting the discontinuation of anti-CMV therapy after patients with quiescent retinitis achieve sustained immune recovery, defined as CD4 counts of ≥100 cells/μL for at least two consecutive visits at least 6 months apart.

Objectives

To review the clinical features, management and outcome of CMV retinitis at Groote Schuur Hospital, Cape Town, SA, over a 10-year period, and to compare treatment protocols of 13 public hospitals in SA that treat patients with CMV retinitis.

Methods

A retrospective record review of patients diagnosed with CMV retinitis between 1 January 2003 and 1 January 2013 was performed. Only patients with polymerase chain reaction (PCR)-proven CMV retinitis were included, and all patients were followed up for at least 1 month. Patients with CMV retinitis who had co-infection with another organism (e.g. syphilis, herpes simplex) were excluded, as were patients in whom a poor fundal view precluded accurate assessment (Table 1).

The following parameters were recorded: age, sex, HIV status and CD4 count (if HIV-positive), presenting and follow-up visual acuity (VA) (best corrected VA), clinical features (macular and optic disc involvement, vitritis, vasculitis and number of retinal quadrants involved), PCR results, dates and number of intravitreal injections of ganciclovir, complications, whether prophylactic argon demarcation laser treatment was performed, and whether the second eye became involved. Best corrected VAs were converted from Snellen to LogMAR for statistical analysis.[11] We subdivided patients into three arbitrary categories according to VA, as follows: category 1 – VA ≥6/18; category 2 – VA 6/24 - 6/60; and category 3 – VA <6/60.

A questionnaire was sent to 13 public hospitals in SA that treat patients with CMV retinitis, with questions on their diagnosis and treatment of the condition.

Ethics approval

Ethics approval was obtained from the University of Cape Town Human Research Ethics Committee (ref. no. 384/2014).

Results

One hundred and forty-one eyes of 91 patients were included in the study. Twenty-seven patients were excluded (Table 1). The median age was 33.6 years (range 14 - 58), and 60.4% (55/91) were female. Fifty patients had bilateral disease. Patients were followed up for a mean of 8.1 months (range 1 - 56). Of these patients, 98.9% (90/91) were HIV-positive, 72.5% (66/91) were on HAART at the time of presentation, and 41.7% (38/91) defaulted from or died during treatment.

Table 1. Patients excluded from the study

Reason for exclusion	*n*
No PCR result	6
Refused treatment	3
Defaulted from treatment	4
Co-infection	6
Inadequate charting	3
Poor fundal view	2
Missing charts	3
Total included	91

PCR = polymerase chain reaction.

Presenting VA of the involved eyes ranged from 6/6 (LogMAR 0.0) to no light perception. Fifty-five percent of eyes had a presenting Snellen VA of 6/60 (LogMAR 1.00) or worse. The presenting and final VAs are summarised in Fig. 2.

The number of intravitreal injections of ganciclovir ranged from 0 to 29 per eye (mean 4.9). There was no association between the number of injections administered and the final visual outcome (Fisher's exact test, p=0.17).

Presenting CD4 counts ranged from 1 to 478 cells/μL (mean 58). There was no statistically significant difference in median final VA when comparing patients who presented with a CD4 count of <50 cells/μL with those with a count of ≥50 cells/μL (χ^2 test, p=0.89).

Seventy-three percent of the patients were on HAART at presentation. These patients had better final VA than those who were not on HAART (p<0.001). However, there was no statistically significant difference when comparing the number of injections needed to achieve disease resolution in patients on HAART with that in patients who were not on HAART (t-test, p=0.97).

Fifty percent of eyes had macular (central 20 degrees of vision) involvement on presentation, and in 48.2% (68/141) the margin of the optic disc was involved. Eyes with macular involvement on presentation had poorer visual outcomes than those in which the macula was spared (t-test, p<0.05). There was also a significant association between the number of retinal quadrants involved and final visual outcome (χ^2 test, p<0.001) (Table 2).

Twenty-two percent of eyes developed retinal detachments. There was no statistically significant association between the number of retinal quadrants involved and the development of retinal detachment (χ^2 test, p=0.40). Presenting CD4 count was also not associated with the development of retinal detachment (χ^2 test, p=0.49).

Presenting VA was a strong predictor of final VA (χ^2 test, p<0.01) (Table 3). Linear regression analysis showed that patients who presented with a VA of ≥6/18 had a 4.6 times higher chance than those who presented with a VA of <6/18 of obtaining a final VA of ≥6/18 (p<0.01).

Responses to the questionnaire

Questionnaires were sent to 13 public health centres in SA that treat CMV retinitis (Table 4). Responses were received from nine centres

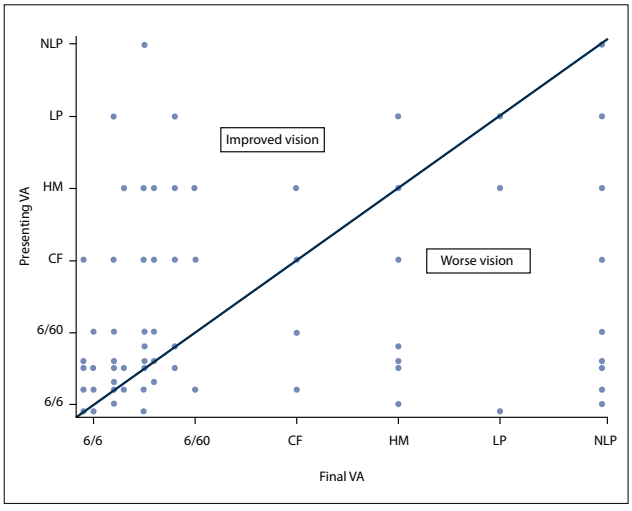

Fig. 2. Distribution of presenting and final VA (logarithmic scale). (VA = visual acuity; NLP = no light perception; LP = light perception; HM = hand movements; CF = counting fingers.)

(69.2%). There was considerable variation in intravitreal ganciclovir injection intervals between centres, ranging from twice weekly to as needed. Follow-up and re-injection criteria also varied.

Six centres had fixed criteria for stopping anti-CMV treatment. They all varied slightly, and none of them strictly adhered to the 1999 US Public Health Service guidelines[10] for the discontinuation of anti-CMV therapy. Three centres did not have fixed criteria, with decisions being made on a patient-by-patient basis. The majority of centres did not perform prophylactic argon demarcation laser treatment. All the centres that responded used intravitreal ganciclovir as the primary treatment for CMV retinitis and referred HIV-positive patients for antiretroviral work-up and treatment.

Table 2. Retinal quadrants v. final VA (*n* (%) of eyes)

	Final VA category			
Number of quadrants involved	1	2	3	Total
1	17 (58.6)	3 (10.3)	9 (31.0)	29 (100)
2	11 (26.8)	14 (34.2)	16 (39.0)	41 (100)
3	4 (33.3)	3 (25.0)	5 (41.7)	12 (100)
4	11 (19.6)	13 (23.2)	32 (57.1)	56 (100)
Total	43 (31.2)	33 (23.9)	62 (44.9)	138* (100)

VA = visual acuity; category 1 = VA ≥6/18; category 2 = VA 6/24 - 6/60; category 3 = VA <6/60.
*Three eyes did not have sufficient charting of this parameter.

Table 3. Presenting VA v. final VA (*n* (%) of eyes)

	Final VA category			
Presenting VA category	1	2	3	Total
1	26 (18.4)	5 (3.5)	6 (4.3)	37 (26.2)
2	10 (7.1)	10 (7.1)	7 (5.0)	27 (19.1)
3	7 (4.9)	18 (12.8)	52 (36.9)	77 (54.6)
Total	43 (30.3)	33 (23.5)	65 (46.2)	141 (100)

VA = visual acuity; category 1 = VA ≥6/18; category 2 = VA 6/24 - 6/60; category 3 = VA <6/60.

Discussion

This retrospective cohort study describes the spectrum of presenting features, clinical course and prognostic factors in patients presenting with CMV retinitis at Groote Schuur Hospital.

Independent risk factors associated with obtaining a better final visual outcome included good presenting VA, fewer retinal quadrants involved, absence of macular involvement and being on HAART at presentation. As would be expected, macular involvement had a significant effect on visual outcome compared with cases in which the macula was uninvolved (*t*-test, $p<0.05$). Presenting CD4 count and the number of injections received had no statistically significant correlation with final visual outcome in our study. In a similar study, patients who were on HAART at baseline had a lower relative risk of losing vision.[12]

We found that patients who were on HAART at the time of presentation had a better mean final VA that those who were not on HAART (*t*-test, $p<0.01$). Several other studies have shown that the introduction of HAART has led to a substantial decrease in the incidence and course of CMV retinitis.[3,6] Similarly, it has been shown that HAART considerably reduced the rate of CMV retinitis adverse events, from 0.35 to 0.14 per 100 patient-days at risk.[13]

All the patients treated during the study period received ocular anti-CMV therapy only, as well as systemic antiretroviral treatment where indicated. A recent study[7] compared patients with CMV retinitis receiving ocular anti-CMV therapy alone with those receiving both ocular and systemic anti-CMV therapy and found a 50% reduction in mortality, a 90% reduction in new visceral CMV and an 80% reduction in involvement of the second eye in the systemic therapy group, although the number of patients in the group that received local treatment only was small ($n=33$).

A significant proportion (41.6%) of our study patients were lost to follow-up, which raises concern about possible missed cases of systemic CMV-related morbidity and mortality. Over the mean follow-

Table 4. Summary of answers to the questionnaire

Centre	Diagnosis	Treatment drug	Treatment regimen	Follow-up	Re-injection criteria	Demarcation laser	CD4 monitoring	ARV referral
1	Clinical + PCR	Intravitreal ganciclovir	Weekly	Re-evaluate	Fundus photo	Yes	Yes	Yes
2	Clinical	Intravitreal ganciclovir	Twice weekly	Set regimen	Fundus drawing	No	Yes	Yes
3	Clinical + PCR	Intravitreal ganciclovir	Weekly	Re-evaluate	Fundus photo	No	Yes	Yes
4	Clinical	Intravitreal ganciclovir	Twice weekly	Set regimen	Fundus photo	No	Yes	Yes
5	Clinical	Intravitreal ganciclovir	Twice weekly	Re-evaluate	Fundus drawing	Yes	Yes	Yes
6	Clinical	Intravitreal ganciclovir	As needed	Re-evaluate	Fundus photo	No	No	Yes
7	Clinical (PCR suspect)	Intravitreal ganciclovir	Weekly	Set regimen	Fundus drawing	No	Yes	Yes
8	Clinical	Intravitreal ganciclovir	Twice weekly	Set regimen	Fundus drawing	No	Yes	Yes
9	Clinical (PCR suspect)	Intravitreal ganciclovir	Weekly	Re-evaluate	Fundus drawing	No	No	Yes

PCR = polymerase chain reaction; ARV = antiretroviral; PCR suspect = PCR performed in cases where the clinical diagnosis is not certain.

up of 8.1 months, 10 patients (11.0%) presented with or developed new visceral CMV. Involvement of the second eye occurred in one of the patients presenting with unilateral disease.

Resource limitations and cost have influenced treatment protocols in developing countries. A study in Singapore showed weekly ganciclovir injections as monotherapy to be an efficacious option for developing countries where newer options of sustained-release implants or oral valganciclovir are unavailable or prohibitively expensive.[13] In the light of the above findings and where resources allow, the addition of systemic anti-CMV therapy should be advocated to decrease morbidity and mortality.

Twenty-two percent of patients in our study developed retinal detachments. A large study of 494 eyes of 379 patients with CMV retinitis found a retinitis-related retinal detachment rate of 16.7%.[14] A further study looked at risk factors for developing retinal detachments in patients with CMV retinitis and found bilateral disease and lesion size to be the strongest predictors.[15] Our study failed to demonstrate an association between the number of retinal quadrants involved and retinal detachment, but we did not specifically measure lesion size. Prophylactic argon retinal photocoagulation has been successful in anecdotal reports and small case series,[16] but there is no uniformity among the centres in SA with regard to treating patients prophylactically with laser.

The decision when to stop anti-CMV therapy has been guided by the international literature, which has identified several important factors including rising CD4 counts, decreasing systemic HIV viral load, duration of HAART and inactivity of CMV lesions. There is a discrepancy among centres in SA regarding the decision when to stop therapy.

Forty-two percent of our patients defaulted from treatment or died during treatment. Patients with CMV retinitis usually have severe immunosuppression and are susceptible to a wide variety of other opportunistic infections. In our patient population, transport difficulties and social stigma are further barriers that may prevent optimal follow-up. Only 58.4% of patients were followed up until discharge from ophthalmology, and injection dates were often missed. Our study is limited further by its retrospective nature. Different clinicians examined patients at each visit, but this was overcome by using photos rather than drawings for comparison.

There is currently no national protocol for initiation, continuation and discontinuation of treatment for CMV retinitis. The only similarities between centres are the use of intravitreal ganciclovir as the mainstay of treatment and vague similarities regarding when to discontinue treatment. The most striking differences are in diagnostic methods (clinical v. PCR), intravitreal injection time interval, monitoring of CD4 counts and criteria for repeat injections.

Conclusions

CMV retinitis in HIV-positive patients is a vision-threatening opportunistic infection that requires aggressive and consistent treatment to preserve visual function. Intravitreal ganciclovir alone is a cost-effective and readily available method of controlling CMV retinitis.

Patients with CMV retinitis are most likely to have favourable visual outcomes when they present with better VA, have fewer retinal quadrants involved, do not have macular involvement and are on HAART. The converse is true for poor visual outcomes. The diagnosis and management of CMV retinitis differ among treatment centres in South Africa

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