

The Demographic Results, Complications and Treatment Outcomes of a CMV (Cytomegalovirus Retinitis) Eye Program

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Abstract

Introduction: Cytomegalovirus (CMV) retinitis is the most significant cause of blindness in patients with HIV infection and is associated with early mortality. Incidence of CMV retinitis declined after introducing HAART and different approaches of anti-viral therapy in CMV retinitis has shown therapeutic efficacy, prevent blindness and reduce mortality. CMV retinitis is now very rare in Western countries and United States. However, it is still an ongoing problem in poor resource countries due to limited facility, lack of screening and antiviral treatment. Although there has been reducing incidence of cytomegalovirus infection in developed world, we believe studies and outcomes of different treatments in this condition should still be reported as CMV is still one of the common infections in immunosuppressed patients who received organ transplants.

Purpose: We would like to report demographic results, treatment outcome and mortality of HIV patients who attended a CMV (Cytomegalovirus Retinitis) eye program in a poor resource country which situated in Southeast Asia in 2015.

Method: Retrospective data analysis of 1828 eyes of 914 patients who attended two district regions in a CMV eye program in a developing country, Myanmar, Southeast Asia.

Results: Incidence of CMV retinitis, Myanmar in 2015 was 1.97%. 50% of patients who underwent screening were already on ART. CMV retinitis among newly diagnosed HIV-infected patients was 38.9%. patients with CMV retinitis were effectively treated by using intravitreal ganciclovir and oral valganciclovir.

Conclusion: Therapy of CMV retinitis by using intravitreal ganciclovir and oral valganciclovir has high efficacy and improves patients survival. It is likely there is a decrease in incidence of CMV retinitis in Myanmar.

Keywords: *Cytomegalovirus Retinitis; Human Immunodeficiency Virus; Intravitreal Ganciclovir; Oral Valganciclovir*

Introduction

According to worldwide figure in 2014, nearly 14 million people suffered human immunodeficiency virus (HIV), and of which 97% were in middle and poor resource countries. Ocular complications of infectious aetiology such as herpes simplex, varicella-zoster, ocular syphilis, ocular tuberculosis and cryptococcal meningitis affect 50 - 75% of cases at some point of their illness [1]. Among them, cytomegalovirus (CMV) retinitis is the most significant cause of blindness in people with HIV-infection [2].

CMV retinitis is now very rare in Western countries following the introduction of HAART and wide spread testing. The incidence of CMV retinitis declined by over 95% in the United States as compared to one third in the pre-HAART era [3]. A 72% reduction in the post-

HAART era as determined in 2012 by the Longitudinal Study of Ocular Complications of AIDS (LSOCA) [19]. However, in poor resource countries as HAART slowly makes its way to them, CMV retinitis is still an outstanding cause of blindness and mortality in immunocompromised patients.

There was a report of 28% mortality rate [4] associated with a diagnosis of CMV retinitis, similar to cryptococcal meningitis mortality [5]. Patients died within 6 months after been diagnosed as CMV retinitis [4], which consistent with previous data showing early mortality in patients with CMV retinitis [6].

CMV retinitis affects a relatively late-stage manifestation of HIV infection when CD4+ cell counts are severely suppressed (e.g. < 50 cells/mm³) [7,8].

Antiviral therapy for HIV related CMV retinitis

Patients with CMV retinitis usually receive systemic, with or without concurrent local therapy as it is part of a systemic infection associated with fellow eye or the other organ involvement.

Ganciclovir, foscarnet and cidofovir were approved by FDA in 1996. All three drugs are selective viral DNA polymerase inhibitors, commenced at induction dose for two to three weeks followed by lower maintenance doses to prevent relapse.

One of the therapies was Ganciclovir and Ganciclovir was administered twice daily at 5 mg/kg IV infusions. The Foscarnet-Ganciclovir CMV Retinitis Trial reveals no difference in efficacy and safety. However, foscarnet showed a survival advantage for patients in the pre-HAART era [9,10]. The efficacy of cidofovir was demonstrated in 1996 by HPMPC trial. Combined therapy of ganciclovir and foscarnet resulted in more toxicity. Cidofovir was a nucleotide analogue with broad antiviral activity, was demonstrated its efficacy in cases previously treated retinitis who had relapsed or were unresponsive to other anti-CMV agents [11].

Valganciclovir, the L-valyl ester, a prodrug of ganciclovir was introduced in 2000, with high oral bioavailability which is 60%. There is another advantage with convenient once-daily dosing, 900 mg once daily for 2 to 3 weeks results in comparable serum ganciclovir levels to those who achieved with daily intravenous induction [12]. Oral valganciclovir has also shown to be equally efficacious in comparative studies with intravenous ganciclovir for induction and maintenance for patients with CMV retinitis.

Induction treatment with intravenous ganciclovir achieved 77% satisfactory response when similar response was achieved in 72% who were assigned to oral valganciclovir [12]. Oral valganciclovir also equally prevents and treats non-ocular CMV as compared to intravenous therapy [13].

A retrospective analysis in 1997 to 2002 has shown that the use of oral valganciclovir has largely surpassed the use of intravenous formulations in cases with CMV retinitis [14].

A Sustained-release implant was approved in 1996 that releases intraocular ganciclovir at 1 µg/hour for up to eight months was found to be very useful to prevent relapse but no longer commercially available, due to decline of incidence of retinitis [15].

In poor resource countries, therapy with intravitreal injection alone was used to reduce the cost of systemic treatment. However, the local therapy alone can lead to higher risk of retinitis in fellow eye and ignores systemic CMV-related disease resulted in higher mortality [16].

Objectives of the Study

To identify active cases of CMV retinitis in HIV patients with CD4 count less than 100 cells/mm³ in a poor resource country in year 2015 and also to study outcomes and complications of treatment with intravitreal Ganciclovir and oral Valganciclovir.

Operational definitions

Cytomegalovirus (CMV) Retinitis: Active CMV Retinitis was diagnosed by presence of active retinitis on clinical examination by using indirect ophthalmoscope.

Venue

The study was performed at two district regions in Myanmar, Southeast Asia.

Materials and Methods

We retrospectively reviewed the clinical records of 914 patients who underwent screening for CMV retinitis based on HIV clinics from March 2015 to December 2015. Patients had clinical examination performed by a trained doctor by using indirect ophthalmoscope.

Patients who were diagnosed with active CMV retinitis underwent treatment with Ganciclovir Intravitreal 4 mg/0.1 mL - administer 2 mg in 0.05 mL (twice weekly for 14 days as an induction)

Sample selection

Inclusion Criteria

Patients diagnosed as HIV infection with CD4 T lymphocyte count less than 100/mm³ were entered in the study. Cases who were or were not receiving ART were included.

Exclusion Criteria

Patients with other ocular comorbidity or pre-existing other retinal diseases were excluded.

Intravitreal ganciclovir injection

The conjunctival cul-de-sac was anesthetized by using minims proxymetacaine hydrochloride (0.5%) eye drops three times. A drop of povidone iodine (5%) was instilled in the cul-de-sac prior to the procedure. The injection was carried out in the treatment room by a trained doctor using aseptic measures and a standardized surgical technique. Ganciclovir Intravitreal 4 mg/0.1 mL - 2 mg in 0.05 ml was administered into the vitreous cavity on supero-temporal quadrant 3.5 to 4.0mm from the limbus.

Statistical analysis

For continuous variables, descriptive variables included the number of patients (N), mean and Standard Deviation (SD) were recorded. For categorical variables, the number and percentage of patients were calculated. The significance level was set at 0.05.

Results

A total of 1828 eyes of 914 patients were found eligible for the study after screening. Mean age of patients was 30.37 +/- 10.7 year. All patients had CD4 T-Lymphocyte less than 100/mm³.

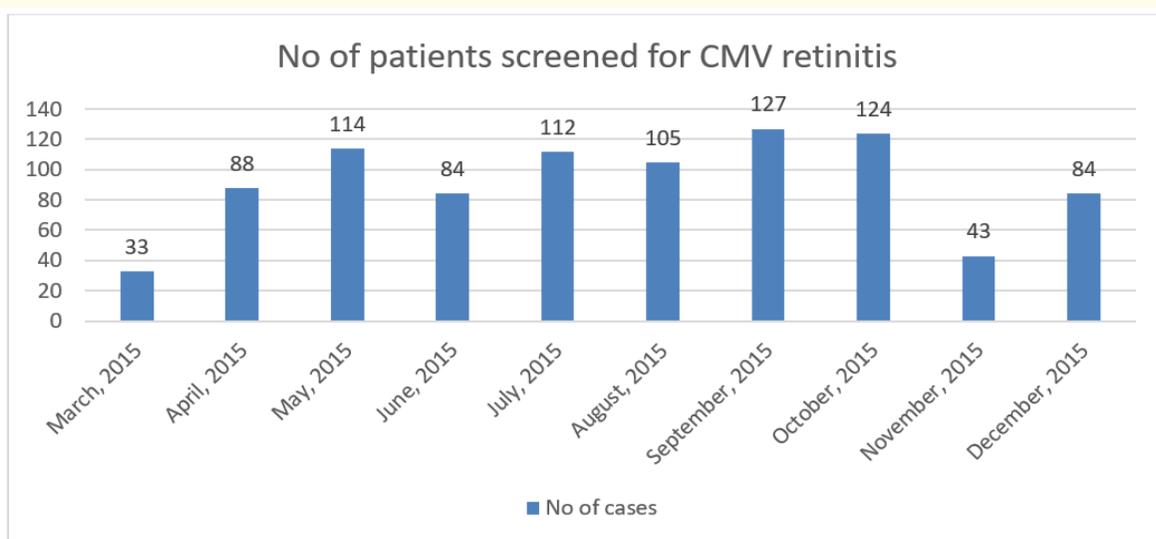


Figure 1: Number of cases screened in each month (n = 914).

CMV retinitis was diagnosed in 18 eyes of 18 patients (1.97% of 914 patients); the majority of patients were male, 66.7% as compared to female which was 33.3%. Male to female ratio was 2:1.

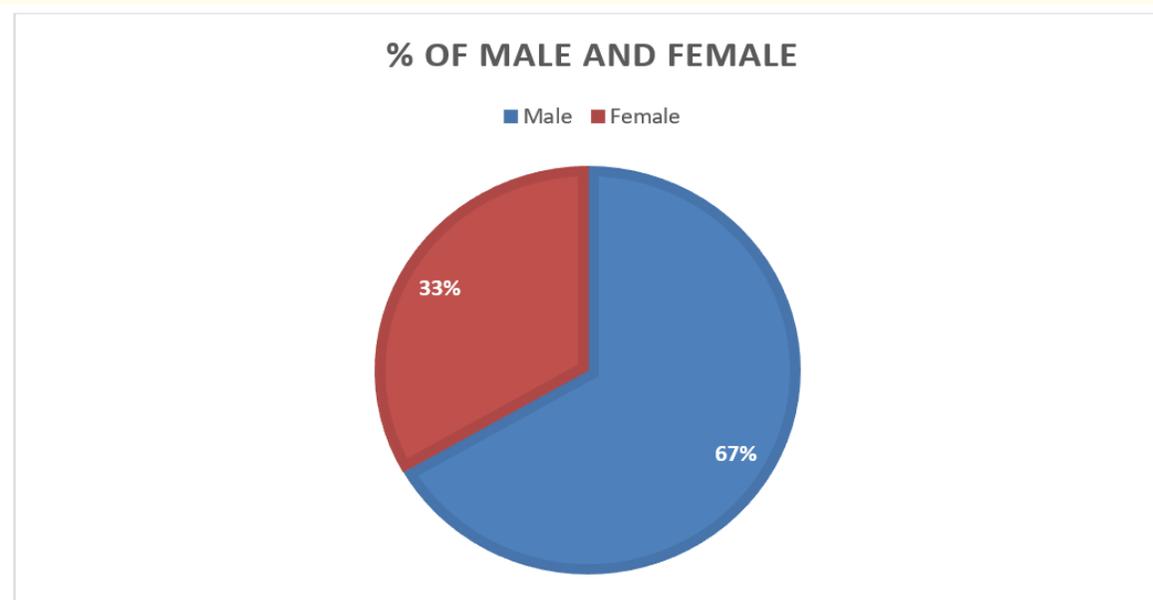


Figure 2: % of male and female patients with active CMV retinitis (n = 18).

Out of 18 patients with active CMV retinitis, 50% were already on first line ART (Antiretroviral treatment) (NNRTI and NRTI) and 38.9% of newly diagnosed cases with HIV-infection also had active CMV retinitis.

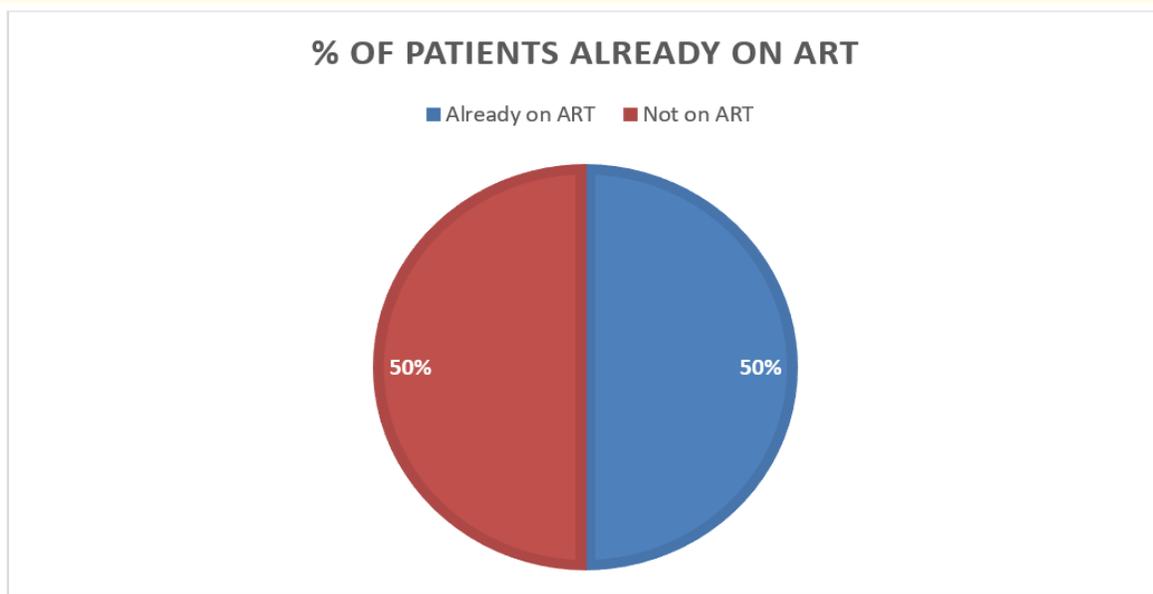


Figure 3: % of cases who were already on ART and not on ART when diagnosed with CMV retinitis (n = 18).

One month after commencing treatment, 73.3% of the cases became improved with their retinitis and 26.7% of eyes with CMV retinitis became inactive. Here, 16.7% of patients did not reach to one month follow up.

On three months follow up, 53.8% of the lesions became inactive and 23.1% of the lesions became improved. However, 23.1% of patients suffered from relapse. Here also 27.8% of the patients did not reach to three months follow up.

On six months, 60% of the lesions became inactive and 40% of the lesions improved well. No further loss from follow up was noted between three and six months.

There was no reported case of endophthalmitis. Five out of 914 patients died (0.55% of all cases who were eligible for CMV retinitis screening). Causes of death were due to occurrence of new opportunistic infections and those patients were also loss to follow up. Death was neither related to extraocular CMV nor directly associated with side effect of oral Valganciclovir (such as bone marrow suppression), according to post mortem that was reports in 5 cases. Mortality rate could be higher if there was adequate information from patients who were lost to follow-up.

Discussion

There was a report on CMV retinitis afflicted 25% to 42% of patients infected with HIV in the pre-highly active antiretroviral therapy (HAART) era [17]. The incidence of CMV retinitis has markedly decreased after introducing ART. Vision loss due to CMV retinitis are mostly due to macula-involving retinitis, immune recovery uveitis and retinal detachment [18].

Developed countries provide resources with HAART and various options of anti-viral therapy in HIV patients with CMV retinitis while the developing world frequently lack components in treatment. Patients may receive substandard of care with higher risk of vision loss and decrease in life expectancy. In Myanmar, one of the Southeast Asia Countries, the incidence of CMV retinitis was 24% in 2006 to 2009 after screening 1782 eyes of 891 new patients and the report was published in 2011 [19]. In some reports, active CMV retinitis was treated by giving one weekly intravitreal ganciclovir for the lack of resources in systemic antiviral therapy. Coverage of ART in those parts of the world is usually slow. Cytomegalovirus (CMV) retinitis caused by a ubiquitous DNA herpes virus causes significant morbidity and mortality in immunocompromised individuals in underdeveloped countries [18].

A report in 2010 highlighted the fact that 90% of HIV-infected people live in the developing countries of sub-Saharan Africa, the Indian subcontinent, Latin America, and Southeast Asia with significant variability among regions and there was also higher prevalence of opportunistic infections such as tuberculosis, pneumocystis pneumonia and cryptococcus [17].

The incidence of CMV retinitis in India varies from 2% in HAART-treated patients to 20%, with the majority of these receiving HAART [20,21]. Biswas., *et al.* reported that 17% of HAART-naïve patients had CMV retinitis [22] and eight years later the same authors reported that the incidence had fallen to 5.7% [23]. The incidence of CMV retinitis in sub-Saharan Africa varies from 0% to 19.6% [24-28]. Nevertheless, the incidence of CMV retinitis is decreasing in majority of the reports.

In our study, we identified the incidence of active CMV retinitis 1.97% in HIV-infected patients with CD4 less than 100/mm³. The percentage has significantly decreased as compared to the incidence 24% in 2006 to 2009 [19]. There was no recorded CMV related mortality in our cases as compared to reported mortality rate of 28% in 2014 [4]. It could be related to HAART therapy received in 50% of patients in our study population. We documented 38.9% of patients with newly diagnosed with HIV-infection were also associated with active CMV retinitis. Treatment for CMV retinitis by using intravitreal Ganciclovir and oral Valganciclovir has shown high efficacy and low risk in HIV related immunocompromised individuals in a poor resource country.

Conclusion

The incidence of active CMV retinitis in a developing country, Myanmar in 2015 was 1.97%, and the incidence was declining although this finding might be different from incidence of other countries with similar situation. Therapy with intravitreal Ganciclovir and oral Valganciclovir has shown high efficacy and is safe to be used in a poor resourced region in which treatment for side effects including bone marrow suppression could be challenging due to lack of one or more facilities. The therapy reduces blindness and improves patient survival.

Conflict of Interest

The authors declare there is no conflict of interest in the study and no funding from any organization and company.

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