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Valganciclovir: A Review of Its Use in the Management of AIDS-Related Cytomegalovirus Retinitis.

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ABSTRACT

Background: AIDS-related cytomegalovirus (CMV) retinitis is one of the most serious ocular complications in individuals with AIDS. It can progress to blindness, and in some cases, be accompanied by potentially fatal systemic disease.Antiviral compounds including Ganciclovir, Foscarnet and Cidofovir are routinely used in the treatment of CMV infection and disease. However, these agents have a poor oral bioavailability and have the inconvenience and expense of intravenous administration. Aim: The aim of the present study was to evaluate the safety and the effectiveness of oral Valganciclovir in the treatment of CMV retinitis in HIV- infected patients. **Methods:** A cohort of 12 CMV retinitis patients with HIV was treated with Valganciclovir at the Department of Ophthalmology, JNIMS during the period of Apr 2013 - Mar 2016. The therapy of Valganciclovir was continued until the CMV retinitis was completely inactive, two reports of CD4+ T lymphocyte counts six months apart was > 100 and the patient was on HAART therapy. The clinical profiles of these patients before and after the therapy were compared. **Results:** On an average the patients received oral Valganciclovir therapy for 9 months. Post- HAART and anti-CMV treatment, Ophthalmology report showed a 1-2 line improvement in Snellens eye chart reading in three patients while among the remaining nine patients, seven had no change in vision and in two patients the eyes went Phthisical and had no perception of light vision (NPL) at the time of last follow up. All the patients had increased CD4 cell counts and remained clinically stable over 8-24 months follow up period. Only minor adverse effects were seen with the treatment. **Conclusion:** Oral valganciclovir therapy is highly effective for the induction and maintenance of AIDS related CMV retinitis . It's used significantly improves the quality of life for patients with this disease as it has eliminated the need for chronic intravenous therapy for people with CMV retinitis.

Keywords: Acquired immunodeficiency syndrome, Cytomegalovirus. Retinitis, Valganciclovir, highly active antiretroviral therapy,Visual acuity.

INTRODUCTION

AIDS-related cytomegalovirus (CMV) retinitis is one of the most serious ocular complications in individuals with AIDS.[1] It can progress to blindness, and in some cases, be accompanied by potentially fatal systemic disease. It is typically caused by reactivation of latent disease. CMV retinitis can be prevented by initiating antiretroviral therapy (ART) early in the course of HIV infection. However, CMV retinitis is still seen in patients who do not have access to these medications and/or are unable to adhere to their ART regimen. Prior to the introduction of highly active antiretroviral therapy (HAART) 30-40% of HIV-infected individuals developed CMV retinitis.[2] However, the introduction of HAART has resulted in a precipitous decline in CMV retinitis infections, which is particularly evident in the developed world. Although the prevalence of CMV retinitis isdecreasing in industrialized countries because of the widespread availability of HAART therapy,10-20% of HIV-infected patients worldwide can be expected to lose vision in one or both eyes as aresult of CMV retinitis. Results of a systematic review of 65 studies published in the online edition of Clinical Infectious Diseases shows prevalence of this AIDS-defining condition as 14% in Asia and 2% in Africa.[1]

Themainstay of diagnosis of CMV retinitis is fundoscopy through adilated pupil.[3] Initial symptoms include visual field defects, the visualization of floaters, flashes and a decline in vision, which initially occurs in one eye.[4] When left untreated, CMV retinitis can progress to retinal detachment withdirect damage to the macula or optic nerve, resulting in permanent blindness. Blindness caused by CMV retinitis is irreversible and can

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occur prior to complete retinal destruction, which was responsible for >90% of HIV-associated blindness in the pre-ART era.[5]As CMV retinitis is asymptomatic inalmost half of affected patients in the early stages of disease,[6] routinescreening fundoscopy for those at high risk of CMV disease by atrained clinician is necessary. WHO has included routine Ophthalmoscopy for all patients presenting for ART initiation with low CD4+ cell counts (<100 cells/µL) in AIDS treatment guidelines.[7,8] At present, the antiviral drugs Ganciclovir, Foscarnet and Cidofovir are commonly used in the treatment of CMV infection and disease.However, these agents have a poor oral bioavailability and have the inconvenience and expense of intravenous administration.Valganciclovir is an oral pro-drug of Ganciclovir, with a 10-fold greater bioavailability than oral ganciclovir. Studies of the pharmacokinetics of valganciclovir among HIV-infected CMV sero-positive patients and liver transplant recipients suggest that it is as efficacious and safe as both oral and IV ganciclovir in immune-deficient patients.

Aim:

The aim of the present study was to evaluate the safety and the effectiveness of oral valganciclovir in the treatment of CMV retinitis in a cohort of 12 HIV-infected patients

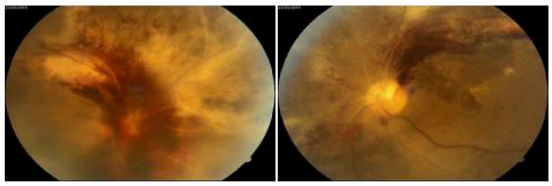
MATERIALS AND METHODS

A total 12 cases of CMV retinitis patients with AIDS were diagnosed and treated at the Department of Ophthalmology, Jawaharlal Nehru Institute of Medical Science (JNIMS), a tertiary referral hospital in North East India during the period of April 2013 to March 2016.All the patients' clinical information at the time of diagnosis including age, gender, ART status, CD4+ T-lymphocyte count, CMV IgM and eyes examination findings were recorded.Fundus examination was done using direct Ophthalmoscope through dilated pupils using Tropicamide 1% and/or Cyclopentolate eye drops 1% with Phenylephrine 2.5% eye drops, biomicroscopy with the slit lamp plus a + 90D lens and indirect ophthalmoscope with +20D lenses. Patients were termed to have retinitis if they had pale or whitish retinal lesions with or without hemorrhages or vasculitis. Patients with retinitis and uveitis were sent to the retina clinic for further examination. The disease is diagnosed presumptively by means of fundoscopy, unlike systemic CMV disease, which requires confirmation by biopsy. Characteristic findings on fundoscopy include dense retinal whitening, haemorrhage, and a typical 'brushfire' retinitis pattern that distributes along blood vessels with small white satellite lesions at the border.CMV retinitis is commonly confused with HIV retinopathy; however, the latter fades and condenses over time while CMV retinitis progresses. Furtherexaminations were performed including visual acuity examination (Snellen Eye Chart reading while standing 20 feet from the chart), fundus photograph (taken to document progression or regression) and the level of CMV IgG and blood CD4 count.

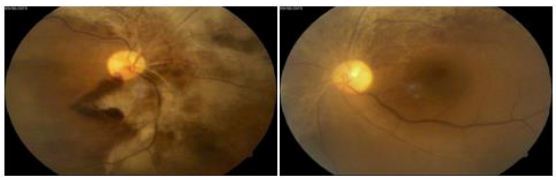
Oral Valganciclovir (VALGAN-450mg, CIPLA) therapy was installed for all the 12 patients with CMV retinitis in combination with HAART therapy. Oral Valganciclovir is more commonly used because it is more convenient and achieves equivalent blood levels equivalent to intravenous administration. 900 mg twice daily induction therapy was given for 21 days followed by 900mg once daily as maintenance therapy.In three patients (Sl. Nos. 4, 10 & 12) with immediately sight-threatening lesions (lesions close to the macula and optic nerve head), intravitreal injection of Ganciclovir 2mg/injection (Cytovene-IV 500mg) with concurrent systemic therapy was done. Complete blood count (CBC) with total and differential counts and serum creatinine levels were checked once a week to identify any hematological adverse events.

Monitoring of response to treatment was done by assessing border activity and position once a week until the retinal lesion was clinically inactive. Follow-up continued at monthly intervals. Photographic monitoring was helpful to detect subtle changes in the border that may indicate progression. With therapy, healing was generally expected in 4 to 6 weeks. The therapy of Ganciclovir was continued until the CMV retinitis was completely inactive, two reports of CD4+ T lymphocyte counts six months apart was > 100 and the patient was on HAART therapy.

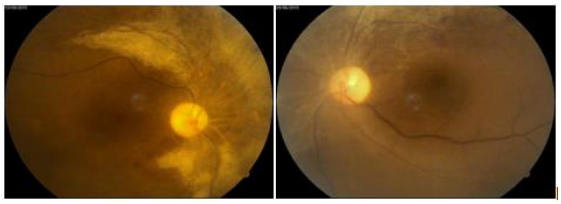
RESULTS



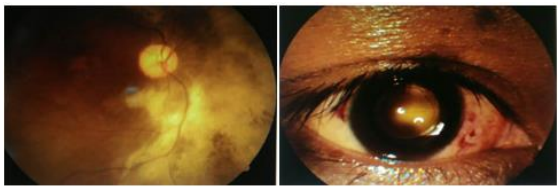
Fundus Photo At The Time Of Diagnosis - March 2015



Fundus Photo After Initiation Of Anti -Cmv Therapy For 3 Months- June 2015



Hemorrhage & Exudation Disappeared Completely After 6 Months-September 2015



Cmv Related Maculopathy And Erm Seen After Cataract Surgery & Iol Implantation – February 2018

The distribution of the patients according to their background and clinical profile at the time of diagnosis before Valganciclovir was initiated is shown in [Table 1]. Twelve patients comprising of seven males (11 eyes) and five females (six eyes) were diagnosed with CMV retinitis with AIDS, four of whom developed bilateral disease. The visual acuity in seven patients was poor (< 6/36 in Snellens eye chart testing) due to involvement of either the optic disc, macular involvement and large size of the retinal lesion (> 30% of the retinal surface area). At the time of diagnosis only four of the 12 patients were on HAART therapy for 2-5 months before initiation of anti-CMV therapy. The reported CD4 count was below 100/ul in all except in one patient (Sl. No.8) at the time of diagnosis

Table 1: Profile of CMV retinitis patients at initial diagnosis

Sl. No.	Age (yrs.)	Sex	Affected eye	CD4 Count	ART status	CMV IgG	Other Co-infection(s)	Visual acuity
1	50	F	LE	32	-ve	+ve	Tubercular lymphadenitis Kaposi sarcoma lips	RE-6/12 LE- 6/60
2	25	M	LE	50	-ve	+ve	No	RE-6/6 LE-6/18
3	35	F	LE	20	+ve for 2 months	+ve	No	RE-6/6 LE-6/12
4	19	M	BE	19	-ve	+ve	No	RE-3/60 LE-3/60
5	33	F	BE	43	+ve for 1month	+ve	No	RE-6/60 LE-6/60
6	32	F	LE	87	+ve for 5months	+ve	No	RE-6/9 LE-6/9
7	27	M	RE	42	-ve	+ve	No	RE-6/12 LE-6/12
8	42	M	LE	149	-ve	+ve	No	RE-6/9 LE-6/9
9	28	M	BE	66	-ve	+ve	No	RE-6/60 LE-6/36
10	20	M	BE	9	+ve for 3 weeks	+ve	MDR TB With severe uveitis RE	RE-PL LE-6/36
11	42	M	LE	57	-ve	+ve	No	RE 6/6 LE 3/60
12	17	F	LE	78	-ve	+ve	Panuveitis LE	RE 6/6 LE PL

Table 2: Clinical profile of CMV retinitis patients with AIDS after Valganciclovir therapy

Sl. No.	Duration of anti-CMV received (months)	Response to anti-CMV therapy	Treatment complications	CD4 count at completion of anti-CMV therapy	Visual acuity at last clinical exam
1	9	Effective	Epiretinal membrane	230	RE-6/12 LE- 6/36
2	9	Effective	-	121	RE-6/6 LE-6/18
3	9	Effective	-	176	RE-6/6 LE-6/12
4	9	Effective	Complicated cataract, CMV maculopathy	200	RE-3/60 LE-6/36
5	9	Effective	Epiretinal membrane	227	RE-6/60 LE-6/60
6	9	Effective	-	180	RE-6/9 LE-6/9
7	9	Effective	-	176	RE-6/12 LE-6/12
8	9	Effective	-	312	RE-6/9 LE-6/9
9	9	Effective	-	134	RE-6/60 LE-6/36
10	9	Not effective	Phthisical (RE)	235	RE-NPL LE-6/36
11	9	Effective	CMV maculopathy	420	RE-6/6 LE-3/60
12	9	Not effective	Phthisical (LE)	299	RE-6/6 LE-NPL

On an average all the patients received oral valganciclovir therapy for 9 months.Post- HAART and anti-CMV treatment, Ophthalmology report showed a 1-2 line improvement in Snellens eye chart reading in three patients while among the remaining nine patients seven had no change in vision and in two patients the eyes went Phthisical and had no perception of light vision (NPL) at the time of last follow up [Table 2]. All the patients had increased CD4 cell counts and remained clinically stable over 8-24 months follow up period.

DISCUSSION

The results of the present study, although limited to a small number of patients, suggest that Valganciclovir can be safely used in treatment of CMV retinitis in HIV infected patients. The medicine was able to control the infection in all the patients in 4 to 6 weeks, as indicated by improvement in the visual acuity by 1-2 lines in Snellens eye chart in 3 patients (25%) and maintained the visual acuity in 7 patients (60%) . When left untreated, CMV retinitis can progress to retinal detachment withdirect damage to the macula or optic nerve resulting in permanent blindness. Two eyes of two patients went phthisical in spite of treatment due to advanced stage of the disease at the time of presentation. The medicine was well tolerated by all the patients and the few adverse events seen during therapy were diarrhea, nausea, vomiting, abdominal pain and headache. However, treatment of CMV retinitis with oral valganciclovir is suppressive but not curative.[9] Valganciclovir profoundly suppresses viral replication, but does not eradicate the virus itself. Cessation of oral Valganciclovir therapy in a profoundly immune-suppressed person results in reactivation of CMV viral replication. Therefore, maintenance therapy is essential in the successful management of CMV retinitis if the patient's immune function remains poor.

A known advantages of systemic therapy with valganciclovir as found out by other researchers is reduction in the incidence of systemic CMV disease.[10] The effectiveness of systemic Ganciclovir is emphasized by the fact that there is an increase of 22–35% in the incidence of new CMV retinitis in the untreated contra-lateral eye with intraocular treatment alone.[11] The convenient administration of Valganciclovir has resulted in better patient-compliance as suggested in a study by Claxton.[12]

CONCLUSION

In summary, the results of the present study corroborate previous reports on the positive outcomes of valganciclovir therapy for the induction and maintenance of CMV disease in HIV-infected patients.Treatment with a simple pill, valganciclovir, is realistic in every setting, whereas the standard of care in low-income and middle-income countries—a weekly intraocular injection of ganciclovir —is inadequate for several reasons and even intraocular injection is unavailable in most settings.However, a simple pill will not entirely solve the problem,[13] and appropriate measures for crucial early detection of cytomegalovirus retinitis in the well-defined vulnerable group of newly diagnosed patients with AIDS (those with CD4 cell counts below 100 cells per μL), are urgently needed.

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