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CLINICAL CHARACTERISTICS OF CYTOMEGALOVIRUS RETINITIS IN HUMAN IMMUNODEFICIENCY VIRUS (HIV) PATIENTS UNDERGOING INTRAVITREAL GANCICLOVIR INJECTION

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ABSTRACT

Introduction: *Cytomegalovirus (CMV) retinitis is the most common ocular opportunistic infection in patients with Human immunodeficiency virus (HIV). The disease is causing blindness and current management commonly characterized by delayed diagnosis and inadequate treatment.*

Purpose: *to describe the clinical characteristic and visual outcome of CMV retinitis with HIV treated with intravitreal ganciclovir injection.*

Methods: *This is a retrospective study included 23 patients (34 eyes) who presented with CMV Retinitis with HIV from January 2020 to July 2023 who received intravitreal ganciclovir in both the induction and maintenance phases until declared cured, characterized by lesion inactivation and CD4+ T-cell counts reaching >100/µL within period of 3 to 6 months. Data were collected including age, gender, affected eye laterality, CD4+ T-cell count at the initial visit at vitreoretinal polyclinic and the 6-month follow-up, total number of intravitreal ganciclovir injections, HAART history at the initial visit, visual acuity at the initial visit, 6-month follow-up, and systemic comorbidities.*

Result*: The median age was 29 years old with 82,6% of them male. Bilateral lesions were observed in 60.9% of the patients. Median CD4 count initial visit was 50 with 52% below 50 cell/µL. Fifteen patients (65,2%) already treated with highly active antiretroviral therapy (HAART) before injection. Tuberculosis was the most common opportunistic infection. Mean intraviteral ganciclovir injection 9,12±3,40 in each eye. Eleven eyes (32.4%) with initial visual acuity ≤1.00 logMAR increased to 19 eyes (55.9%) at the 6-month follow-up. There were statistically significant difference between baseline visual acuity and 6-months follow up after intravitreal ganciclovir. (p= 0,008).*

Conclusion*: Retinitis cytomegalovirus tend to have more severe clinical presentations in patients with CD4 counts below 50 cells/µL. Intravitreal ganciclovir is effective in controlling CMV retinitis.*

Keywords: Cytomegalovirus retinitis; HIV; Ganciclovir intravitreal
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INTRODUCTION

Cytomegalovirus (CMV) retinitis is the most common opportunistic ocular infection, leading to blindness in patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)[1]. Infections typically arise when CD4+ T-cell counts are below 200/µL, and current clinical management is often faced with delayed diagnosis and inadequate therapy[2,3].

One million three hundred thousand people globally were infected with HIV in 2022[4]. The incidence of CMV retinitis is 20-40% in patients with HIV, with 90% experiencing blindness[1,4]. A study in Myanmar in 2019 revealed a prevalence of CMV retinitis in patients with HIV/AIDS and CD4+ counts <100 cells/µL at 10.7%[5]. A descriptive study at Cicendo Hospital from 2015 to 2017 reported that of 162 patients diagnosed with HIV, 14.81% had CMV retinitis[6].

CMV retinitis is a clinical diagnosis that varies among patients and is characterized by hemorrhage and full-thickness retinal necrosis along the arcade of retinal blood vessels. Common complaints include floaters, photopsia, and decreased visual acuity[7]. Location lesions in the posterior pole with involvement of the macula, optic nerve, or retinal detachment, can threaten visual acuity[7,8].

Intravitreal ganciclovir is administered in cases of CMV retinitis with vision-threatening lesions, especially those close to the macula or optic nerve, and in patients with contraindications or side effects from systemic therapy. Intravitreal ganciclovir injections effectively achieve high concentrations in the vitreous with minimal systemic toxicity[7,8].The therapeutic protocol is divided into two phases. The induction phase involves administering 2 mg twice a week for 2-3 weeks to suppress virus replication, followed by the maintenance phase once a week to suppress virus activity. This regimen is continued until there is clinical improvement, such as lesion inactivation and CD4+ T-cell counts reaching >100/µL, within a 3 to 6-month period. Complications of intravitreal injections include endophthalmitis, vitreous hemorrhage, and retinal vascular obstruction[8,9]. Intravitreal gancyclovir therapy is suitable for most of the patient in Cicendo Hospital due to cost effectiveness in line with socioeconomic conditions in developing countries, covered by health insurance, more readily available and safe procedure with local side effects.

The incidence of CMV retinitis has been reported to decrease with Highly Active Antiretroviral Therapy (HAART)[2]. HAART in HIV patients reduces the incidence of CMV retinitis in developed countries by 80–90%. However, in developing countries, patients are often diagnosed in the late stages with low CD4 counts, making CMV retinitis a persistent major issue. This is also observed in Southeast Asia, including Indonesia, where CMV retinitis in HIV/AIDS patients remains a leading cause of blindness[10,11].

The objective of this study is to provide an overview of the clinical characteristics of CMV retinitis in HIV patients undergoing intravitreal ganciclovir injection therapy at the National Eye Center of Cicendo Hospital. This information can serve as a basis for selecting therapy for CMV retinitis patients, as well as for educational material and further research, provides data on the success rate of CMV retinitis management at the National Eye Center of Cicendo Hospital.

METHODS

This study is retrospective descriptive study utilizing secondary data from patients' medical records at the Vitreoretina polyclinic of the National Eye Center, Cicendo Eye Hospital, Bandung, from January 2020 to July 2023. The study has been approved by the Committee of Medical Research Ethics of Cicendo Eye Hospital, Bandung with number DP.04.03/D.XXIV.16/12569/2023.

The inclusion criteria for this study consist of new patients from the vitreoretinal polyclinic diagnosed with CMV retinitis and HIV-positive who have undergone intravitreal ganciclovir injection in both the induction and maintenance phases until declared cured, characterized by lesion inactivation and CD4+ T-cell counts reaching >100/µL within period of three to six months. The exclusion criteria consist of incomplete medical record data and patient lost to follow up.

Data were collected from medical records, including age, gender, affected eye laterality, CD4+ T-cell count at the initial visit to the vitreoretinal clinic and the 6-month follow-up, total number of intravitreal ganciclovir injections, HAART history at the initial visit, visual acuity at the initial visit and 6-month follow-up, and systemic comorbidities.

Visual acuity data were presented as logarithms of the minimum angle of resolution (logMAR). Snellen visual acuity was converted to logMAR to facilitate numerical analysis for statistical evaluation.

STATISTICAL ANALYSIS

The data obtained were inputted into work tables and analyzed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Demographic and clinical characteristics were analyzed descriptively. Normality tests for data, specifically the Shapiro-Wilk test for initial LogMAR visual acuity and 6-month follow-up, were conducted. The normality test results indicated that the data were not normally distributed. Analysis to determine the difference in visual acuity at baseline and 6-month follow-up after therapy was conducted using the McNemar test.

RESULTS

Based on medical record data collected from January 2020 to July 2023, this study found 34 eyes from 23 patients were diagnosed with CMV retinitis and HIV. Table 1 illustrates the demographic characteristics of the patients. The median age of the patients was 29 years (range: 23-53 years), the majority were in the 20-29 years old (47.8%). There are more male patients than female patients. Table 2 illustrates the clinical characteristics. Of these results, 14 patients (60.9%) had bilateral involvement, and 9 patients (39.1%) had unilateral involvement. Initial visual acuity at the clinic visit showed that 23 eyes (67.6%) had >1.00 logMAR, and 11 eyes (32.4%) had ≤1.00 logMAR. Six patients had retinal detachment, and 2 patients had unilateral optic atrophy. Visual acuity at the 6-months follow-up after intravitreal ganciclovir injection revealed 15 eyes (44.1%) with >1.00 logMAR and 19 eyes (55.9%) with ≤1.00 logMAR.

A total of 34 eyes received 303 injections, with an average injection 9.12±3.40 peach eye. Bilateral injections were administered to 22 eyes, while 12 received unilateral injections. Fifteen patients (65.2%) were already receiving HAART therapy at the time of CMV retinitis diagnosis. The median CD4 count at the initial visit was 50 cells/µL, majority 52.2% (12 patients) having CD4 counts ≤50 cells/µL. The median CD4 count at the 6-months follow-up was 176 cells/µL, with 22 patients having CD4 counts >100 cells/µL and only 1 patient with a CD4 count of 56 cells/µL. Three patients received intravitreal ganciclovir injections with CD4 counts >100 cells/µL.

Table 3 indicates systemic diseases in this study, including tuberculosis in 6 patients (20.1%), with 5 patients under treatment and 1 patient completing

therapy in 6 months. Syphilis was present in 4 patients (17.4%).

Table 4 demonstrates that in both groups HAART status, there was an improvement in visual acuity at the 6-month follow-up after injection therapy.

A total of 34 eyes from 23 patients received therapy in this study. Data analysis revealed a significant difference between initial visual acuity and the 6-month follow-up after therapy. Eleven eyes (32.4%) with initial visual acuity ≤1.00 logMAR increased to 19 eyes (55.9%) at the 6-month follow-up after therapy, as presented in Table 5.

Table 3**. Systemic diseases in CMV+HIV**

Disease	Total (n=23)
Tuberculosis	6 (20,1%)
Syphilis	4 (17,4%)
No systemic diseases	13 (56,5%)

Table 4**. HAART status prior injection and improvement visual acuity at 6-month follow up**

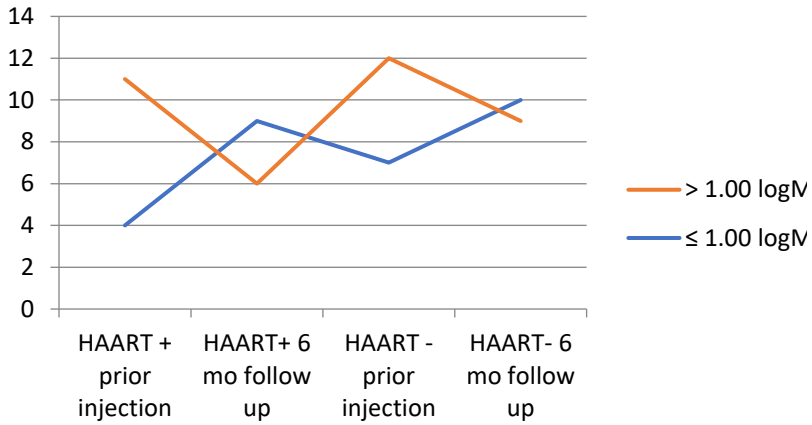

Table 1**. Demographic Characteristics**

Variabel	Frequecy (n=23)
Median Age (year)	29
20-29	11 (47,8%)
30-39	8 (34,8%)
40-49	3 (13,0%)
>50	1 (4,3%)
Male	19 (82,6%)
Female	4 (17,4%)

Table 2**. Clinical Characteristics**

Variabel	Frequency
Laterality (n=23)	
Unilateral	9 (39,1%)
Bilateral	14 (60,9%)
Status HAART prior injection (n=23)	
HAART (+)	15 (65,2%)
HAART (-)	8 (34,8%)
Initial CD4 count (n =23)	
≤50 sel/µL	12 (52,2%)
>50 sel/µL	11 (47,8%)
Median Initial CD4 count (sel/µL)	50 (5-249)
CD4 Count at 6-month follow-up (n =23)	
>50sel/µL	23 (100%)
Median CD4 Count at 6-month follow-up	176
Average number injections 9,12±3,40	
Initial Visual Acuity (n=34)	
≤1.00 logMAR	11 (32,4%)
>1.00 logMAR	23 (67,6%)
Visual Acuity at 6-month follow-up (n=34)	
≤1.00 logMAR	19 (55,9%)
>1.00 logMAR	15 (44,1%)

Table 5**.** Difference in initial visual acuity and 6-month follow-up after Intravitreal Ganciclovir

Initial visual Acuity	Visual Acuity at 6-month follow-up		Total
	≤ **1.00 logMAR**	>1.00 logMAR	
≤1.00 logMAR	11	-	11 (32,4%)
> 1.00 logMAR	**8**	15	23 (67,6%)
Total	19 (55,9%)	15 (44,1%)	34 (100%)

Description: Chi-square Mc.Nemar = 0,008

DISCUSSION

The therapeutic goal for CMV retinitis is to maintain and reduce the risk of vision-related complications.

In this study, most patients were in the 20-29 age group (47.8%), with a higher proportion of males (82.6%) than females. These findings align with research conducted by Ali et al[13]. in Qatar, Singh et al[10]. in India, and Naryati et al[3]. in Indonesia where the average age varied from 30-40 years, and the male proportion more than 50%. According to the Health Ministry's Center for Data and Information (infoDATIN)[18] in 2022, there were

22,331 cases of HIV/AIDS in Indonesia, with 68.1% occurring in the age group of 25-49 years and 70% being male. The predominant risk factors were associated with sexual contact, sexually transmitted infections, and intravenous drug use.

This study found the highest CD4 count of ≤50 cells/μL in 12 patients (47.8%). Similar findings have been reported by Leenasirimakul et al[11]., Xaverina et al[12]., Ali et al[13]., and Sovani et al[6]., indicating that the CD4 count in patients at the initial diagnosis ranged from 50-100 cells/μL. The Longitudinal Study of Ocular Complications of AIDS (LSOCA) states that a CD4 count <50 cells/μL is a crucial risk factor for the occurrence of CMV retinitis in opportunistic infections and the final manifestation of HIV. This serves as a marker for screening CMV retinitis in HIV/AIDS patients. Patients with HAART failure and extraocular CMV infection have a poor prognosis and an increased risk of CMV infection recurrence[2,10].

All patients in this study came for treatment with complaints of decreased visual acuity and floaters. Initial visual acuity >1.00 logMAR (<20/200) was found in 23 eyes (67.6%). Six patients had retinal detachment, and 2 patients had unilateral optic nerve atrophy. Most CMV retinitis patients presenting to Cicendo Hospital were initially diagnosed with poor visual acuity. In developing countries, patients often seek healthcare when their vision has significantly deteriorated, or the disease manifests in both eyes. Several factors causing this in developing countries, including inadequate socioeconomic conditions, lack of disease-related education, and difficulty accessing healthcare facilities, contribute to delayed medical intervention[11,12]. Blindness in CMV retinitis is attributed to persistent full-thickness retinal necrosis, with lesions in the posterior pole involving the macula, optic nerve, or retinal detachment[7,8]. The multicenter tertiary care study by Orlin et al[14]. reported bilateral retinal detachment in 16.7% of CMV retinitis patients. Iu et al[15]. stated that visual acuity <20/200 with macular involvement is a poor prognostic factor, where most lesions progress to atrophy, causing permanent visual impairment.

The administration of HAART is crucial to slowing the progression of the disease by suppressing HIV replication, improving the immune system, and reducing the incidence of opportunistic infections, thereby increasing the count of CD4+ T cells[16,]. The combination of HAART and anti-CMV therapy significantly reduces the incidence and morbidity of CMV retinitis and the risk of retinal detachment by up to 95%[20]. Doan et al. demonstrated that the incidence of CMV retinitis in HIV patients before the introduction of HAART was 6.1%, and it decreased to 1.2% in the HAART era[2]. A study by He et al. in China reported a decrease in the bilateral blindness rate due to CMV retinitis (visual acuity <20/200) from 14.8/100 persons per year to 0.4/100 persons per year with the use of HAART [19]. Study by Singh et al., 65.4% of CMV retinitis patients had a CD4 count ≤50 cells/μL and a history of HAART administration[10]. In this study, 15 patients (65.2%) with CMV retinitis had a history of HAART administration and a CD4 count ≤50 cells/μL. Cases of CMV retinitis persist in the HAART era, estimated at around 69%, characterized by consistently low CD4 counts, attributed to delayed diagnosis, HAART failure, or non-compliance with treatment[2,16,24].

This study demonstrates an improvement in visual acuity at the 6-month follow up in both groups with a history of HAART administration before injection. To the best of our knowledge, this journal is the first to present the results of intravitreal ganciclovir monotherapy in CMV retinitis patients with HIV, considering the HAART status and clinical outcome.

The most common systemic disease in this study was tuberculosis, aligning with Sovani et al[6]., where the majority of accompanying systemic disorders were tuberculosis. HIV infection with

severe immunodeficiency leads to multi-organ systemic disorders, serving as a poor prognostic factor and posing a high risk of mortality[22].

In this study, a significant difference was observed among the 34 eyes that received therapy between the initial visual acuity and the 6-month follow-up after treatment (p=0.008; McNemar test). Data analysis revealed that 11 eyes with an initial visual acuity of ≤1.00 logMAR improved to 19 eyes (55.9%) at the 6-month follow-up, with 8 eyes showing visual acuity improvement, 26 eyes maintaining their visual acuity, and 1 eye experiencing a decrease in visual acuity due to rhegmatogenous retinal detachment. Xie et al.'s research in China reported an increase in visual acuity in 32 eyes with CMV retinitis and HIV after intravitreal ganciclovir injection during the induction phase, with maintenance over a three-month follow-up, averaging 5.03 injections per eye[21]. Agarwal et al.'s study mentioned that 53.84% of HIV patients with CMV retinitis showed lesion improvement after 1 month of intravitreal ganciclovir injection, and no lesion progression was observed[17]. There were no complication of the intravitreal injections in this study, such as endophthalmitis, vitreous hemorrhage, and retinal vascular obstruction .

This study has several limitations, including a relatively small sample size, incomplete medical record data covering the type and zone of CMV retinitis lesions, and the need for fundus photo documentation before and after the procedure to assess treatment response criteria objectively. Therefore, future research is recommended to include a prospective study design, a larger sample size, a more extended evaluation period to assess treatment outcomes, and additional clinical characteristics of CMV retinitis.

CONCLUSION

CMV retinitis tends to present more severe clinical features in patients with CD4 counts ≤50 cells/μL. Intravitreal ganciclovir injections are effective in controlling CMV retinitis with minimal complications.

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