

Effect of individualized therapy for AIDS patients with cytomegalovirus retinitis in intravitreal ganciclovir injections

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Received: 2019-02-12 Accepted: 2019-04-22

Abstract

• **The effect of intravitreal ganciclovir injection combined with intravenous infusion on acquired immune deficiency syndrome (AIDS) patients with cytomegalovirus retinitis (CMVR) was investigated. A total of 32 eyes in 23 AIDS patients diagnosed as CMVR from 2017 to 2018 were included in the retrospective study. All patients underwent induction therapy by using intravenous drip of the anti-cytomegalovirus (CMV) agent ganciclovir (5 mg/kg q12h) combined with intravitreal ganciclovir injection (3 mg/time, 2 times/wk). The visual acuity, fundus photographs, lesion location, and number of intravitreal injections were observed preoperatively and postoperatively. Totally 14 eyes were cured during induction therapy. The number of injections [4.13 (2 to 6)] in CMVR patients with peripherally fundus lesions were significantly lower than those with central lesions [4.89 (2 to 6)]. The individualized therapy of intravitreal ganciclovir injections for AIDS patients with CMVR can effectively reduce the numbers of intravitreal injections.**

• **KEYWORDS:** cytomegalovirus; retinitis; acquired immune deficiency syndrome; ganciclovir; intravitreal injection; monotherapy

DOI:10.18240/ijo.2019.08.19

Citation: Xie LY, Chen C, Kong WJ, Du KF, Guo CG, Dong HW, Wei WB. Effect of individualized therapy for AIDS patients with

cytomegalovirus retinitis in intravitreal ganciclovir injections. *Int J Ophthalmol* 2019;12(8):1351-1355

INTRODUCTION

Cytomegalovirus retinitis (CMVR) is the most common opportunistic infection of the eye in acquired immune deficiency syndrome (AIDS) patients. It's a common cause of vision loss, with an incidence of about 10% to 40% in AIDS patients^[1-6]. Cytomegalovirus (CMV) infection is a major cause of morbidity and mortality in immunocompromised hosts^[7]. CMVR is characterized by typical, progressive, necrotizing retinitis and retinal vasculitis with yellow-white lesions and flaky hemorrhage along the blood vessels, and is also known as "cheese- and ketchup-like retinitis"^[8]. Cohort studies have shown that in the modern era of antiretroviral therapy, the visual prognosis of AIDS and CMV retinitis patients has significantly improved^[9-11]. At present, the research on CMVR treatment of AIDS patients in China mainly focuses on the efficacy of ganciclovir or sodium phosphate intravenous drip and intravitreal injections. Sometimes it involves intravenous drip combined with local intravitreal ganciclovir for the treatment of diseased eyes. In most studies, intravitreal injections were administered twice a week during the induction period for three weeks, and then once a week during the maintenance period.

Although intraocular medications are usually well-tolerated, AIDS patients are already in the final stage of HIV infection, which invades the immune system and eventually leads to defects in cellular immune function, causing various opportunistic infections. In consideration of the most AIDS patients with CMVR have CD4+ T-lymphocyte counts <50 cells/ μ L and multiple systemic opportunistic infections. Repeated intraocular injection may increase risk of endophthalmitis. In this study, we investigate the effect of individually intravitreal ganciclovir injection combined with intravenous infusion in the treatment of CMVR in AIDS patients.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethics Committee of Beijing YouAn Hospital Affiliated to Capital Medical University and complied with the Helsinki Declaration. Written informed consent was obtained from each patient.

General Information A total of 32 eyes in 23 AIDS patients [20 males and 3 females, with a mean age of 34.78 ± 7.19 y (range 20-50)] diagnosed with CMVR who were treated in Beijing YouAn Hospital of Capital Medical University from February 2017 to October 2018 were included in the study. Nine patients were diagnosed with CMVR in both eyes and 14 patients in one eye. Four patients received highly active antiretroviral therapy (HAART). Twenty patients developed opportunistic infections such as tuberculosis and pneumonia. All patients had CD4+ T-lymphocyte counts <50 cells/ μ L.

Diagnostic Criteria AIDS was diagnosed according to the criteria specified in the Third Edition of the Guidelines for Diagnosis and Treatment of HIV/AIDS (2015)^[12] in the Infectious Disease Department of the hospital. CMVR was diagnosed in agreement to the AIDS Clinical Trials Group (ACTG) criteria based on the observed characteristic retinal changes of the fundus by experienced ophthalmologists. And if necessary, CMV DNA detection in the anterior aqueous humor could be performed to make a definite diagnosis. Progression of CMVR was recorded by fundus photography.

Exclusion Criteria The rules for excluding eyes and patients in this study are as follows: 1) patients who had received anti-CMV treatment in the past; 2) eyes with retinal detachment or no light perception; 3) patients with glaucoma, cataracts, and other serious eye diseases; 4) eyes with necrotizing retinitis caused by varicella-zoster virus, herpes simplex virus, syphilis, toxoplasmosis or lymphoma.

Clinical Examinations All patients underwent best-corrected visual acuity (BCVA; logMAR visual acuity), intraocular pressure (IOP), slit lamp, mydriatic fundus, and fundus photography examination (with a panoramic ophthalmoscope Optos Daytona) before and after intravitreal injection.

Therapeutic Interventions All patients underwent anti-CMV induction therapy by intravenous dripping of ganciclovir with a dose of 5 mg/kg *q12h* for three weeks, combined with intravitreal ganciclovir injections with a dose of 3 mg (2 times per week) depending on the patient's fundus changes. Fundus examination was performed on the second day after each intravitreal injection of ganciclovir. The fundus was examined by two experienced doctors. During induction therapy, both doctors considered that the patient has been cured clinically, the intravitreal injections can be stopped. After 3-week induction therapy, each patient underwent maintenance therapy by oral administration of 1 g ganciclovir, 3 times per day. Vitreous injection therapy is based on the quality control standards of retinopathy in China^[13].

Therapeutic Efficacy Assessment The effect of therapeutic intervention was divided into three levels: 1) invalid: enlarged lesion with new bleeding and exudation; 2) effective: no enlargement of the lesion area and no new bleeding or

exudation; 3) clinical cure: absorption of bleeding and exudation and scarring of the lesions. All therapeutic effects were judged by two experienced doctors.

Fundus Lesion Classification in Cytomegalovirus Retinitis According to the distance of the lesions from the macula, the lesions were divided into two types: central lesions within a distance of 1500 μ m and peripheral lesions at a distance >1500 μ m^[14-15].

Statistical Analysis Statistical analysis was performed by SPSS (version 18.0, USA). Descriptive analysis was performed for BCVA, number of injections, with categorical variables summarized with frequencies and percentages and continuous variables summarized as either means with standard deviations or medians with ranges.

RESULTS

Therapeutic Efficacy The 32 diseased eyes of the 23 patients showed a decrease in lesion range, without new bleeding or exudation after treatment. As shown in fundus photographs, the objective response rate (ORR) was 100%. Totally 14 eyes (44%) were clinically cured (5 eyes from the central-lesion class and 9 eyes from the peripheral-lesion class). For 18 eyes (56%), fundus treatment was effective (12 eyes from the central-lesion class and 6 from the peripheral-lesion class; (Figures 1 and 2).

Best Corrected Visual Acuity In patients with central fundus lesions, the BCVA (logMAR visual acuity) were 1.56 (0.20 to 2.30) and 1.00 (0.00 to 1.85) (before and after treatment) respectively ($P=0.000$). In patients with peripheral fundus lesions, the BCVA were 0.52 (0.20 to 1.00) and 0.19 (0.00 to 0.50) (before and after treatment) respectively ($P=0.000$). In short, all patients improved BCVA after treatment, and the difference in BCVA between before and after treatment was statistically significant.

Number of Injections The 32 eyes were received 161 intravitreal injections, an average of 5.03 injections per eye. Each of the 17 eyes in CMVR patients with central fundus lesions were received an average of 4.89 (2 to 6) injections (2 eyes injected less than 6 times and 15 eyes injected 6 times). Totally 15 eyes in CMVR patients with peripheral fundus lesions received an average of 4.13 (2 to 6) injections (9 eyes injected less than 6 times and 6 eyes injected 6 times). These results indicated that the number of injections in CMVR patients with peripheral lesions was significantly lower than those with central lesions ($P=0.028$; Table 1, Figure 3).

Follow-up Observation After 3wk induction therapy, all patients were switched to maintenance therapy of oral ganciclovir administration with a dose of 1 g, 3 times per day. Clinical follow-up observation was carried out in patients with improved condition. All patients were cured clinically within three months. Only one patient developed rhegmatogenous retinal detachment after 6mo.

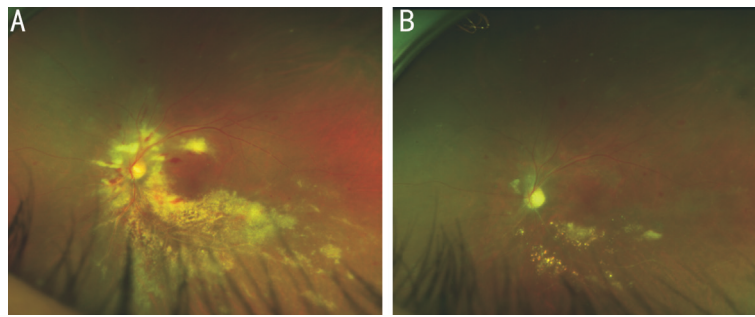


Figure 1 The fundus condition of CMVR patient with central lesions A: Before the treatment; B: The patient received 3wk induction therapy by intravitreal injection (6 times) combined with intravenous dripping.

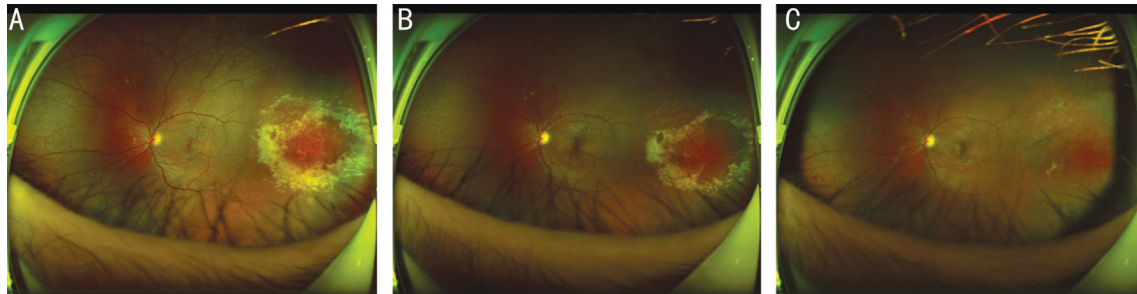


Figure 2 The fundus condition of CMVR patient with peripheral lesions A: Before the treatment; B: The patient improved obviously after 3-week induction therapy by intravitreal injection (6 times) combined with intravenous dripping in fundus lesions, bleeding and exudation; C: The patient underwent oral administration of ganciclovir for one month after induction therapy.



Figure 3 The fundus condition of CMVR patient with peripheral fundus lesions A: Before the treatment; B: The patient received two intravitreal injections of ganciclovir and no further injections.

Table 1 Number of injections in the 32 eyes of 23 patients

| Parameters | Central fundus lesions | | | Peripheral fundus lesions | | | |
|-------------------|------------------------|---|----|---------------------------|---|---|---|
| No. of injections | 2 | 4 | 6 | 2 | 3 | 4 | 6 |
| No. of eyes | 1 | 1 | 15 | 1 | 3 | 5 | 6 |

Complications No one had serious complications such as endophthalmitis. Two cases of IOP transiently elevated, and improved after anterior chamber paracentesis and other relevant treatments. Five patients developed subconjunctival hemorrhage which spontaneous remission without special treatment.

DISCUSSION

Each patient in this study simultaneously underwent induction therapy with intravenous ganciclovir injection and received intravitreal ganciclovir injections. Intravenous ganciclovir can help to control systemic CMV and reduce mortality. Intravenous ganciclovir is designed to prevent monocular

diseases from becoming binocular diseases and to inhibit the development of extraocular CMV disease. Intravitreal ganciclovir injection can effectively increase the drug concentration in CMVR lesions without increasing systemic toxicity and side effects. The traditional treatment is intravitreal ganciclovir induction therapy with twice a week for three weeks, followed by maintenance therapy with intravitreal ganciclovir injections once a week^[16]. In addition, it was reported that patients received ganciclovir intravitreal injection four times a week^[17], or 1-week intervals for two months^[18]. Although intraocular drugs are generally well tolerated, it is not convenient for patients to receive such treatment.

This treatment is especially suitable for AIDS patients, who usually have multiple systemic or opportunistic infections. The potential complications of intraocular injection include endophthalmitis, vitreous hemorrhage and retinal vascular obstruction. Additionally, retinal detachment increased with the number of injections, and the frequency of injection increased accordingly^[19]. Although intravitreal ganciclovir monotherapy can provide high concentration in intravitreal antiviral drugs to effectively control intraocular infections, it doesn't prevent other eye infections and the occurrence of systemic CMV disease^[20]. Therefore, each patient in this study received intravitreal ganciclovir injection based on systemic induction therapy, and stopped intravitreal injection according to the fundus of the eye, so as to reduce the number of intravitreal injection and the risk of related complications in some patients. In this study, the average number of injections for CMVR patients with central fundus lesions was 4.89 (2 to 6) and for CMVR patients with peripheral fundus lesions was 4.13 (2 to 6). The latter was significantly lower than the former, which may be due to the tendency of CMVR not extending to macula. The pathological changes involving macular and optic nerves are more serious, so the average number of injections in patients with central fundus diseases is greater than that in patients with peripheral fundus diseases.

In induction therapy, 14 eyes were clinically cured and 18 eyes were effective. During the follow-up period, only ganciclovir was given orally, and all patients were cured within 3mo.

Whether central or peripheral fundus lesions, CMVR patients got clinical cure in twice injection. In 2 patients with central fundus diseases and 9 patients with peripheral fundus diseases, good therapeutic effects were observed even if 6-time intraocular injection induction treatments were not completed.

This is only a retrospective observational study without strict control groups as in prospective studies, which must be improved in our future studies to find the optimal regimen.

In conclusion, when AIDS-related CMVR patients receive induction therapy by intravenous injection, it is necessary to give ganciclovir in vitreous alone according to the fundus condition of the patients. In our clinical work, It is important to make a distinction between central and peripheral fundus lesions in CMVR patients, then we can use an individual therapy, instead of the traditional treatment which is intravitreal ganciclovir induction therapy with twice a week for three weeks. So, we hope that all CMVR patients can effectively reduce the number of intravitreal injection and achieve satisfactory therapeutic effect.

ACKNOWLEDGEMENTS

Foundations: Supported by the Open Research Project of Key Laboratory of Capital Medical University (No.2017YKSJ04);

Capital Medical University Fundamental Clinical Research Cooperation Fund (No.16JL73).

Conflicts of Interest: Xie LY, None; Chen C, None; Kong WJ, None; Du KF, None; Guo CG, None; Dong HW, None; Wei WB, None.

REFERENCES

- 1 Sugar EA, Jabs DA, Ahuja A, Thorne JE, Danis RP, Meinert CL; Studies of the Ocular Complications of AIDS Research Group. Incidence of cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol* 2012;153(6):1016-1024.e5.
- 2 Holland GN. AIDS and ophthalmology: the first quarter century. *Am J Ophthalmol* 2008;145(3):397-408.
- 3 Jabs DA. AIDS and ophthalmology, 2008. *Arch Ophthalmol* 2008;126(8):1143-1146.
- 4 Wang ZL, Jia RB, Ge SF, He TW, Zhang YZ, Yang YL, Wang YF, Shi WD, Ji YR, Ye FX, Chen P, Lu JF, Sun J, Xu XF, Zhou YX, Gu P, Luo M, Lu HZ, Fan XQ. Ocular complications of human immunodeficiency virus infection in Eastern China. *Am J Ophthalmol* 2012;153(2):363-369.e1.
- 5 Ausayakhun S, Watananikorn S, Ittipunkul N, Chaidaroon W, Patikulsila P, Patikulsila D. Epidemiology of the ocular complications of HIV infection in Chiang Mai. *J Med Assoc Thai* 2003;86(5):399-406.
- 6 Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. *Lancet* 2014;384(9939):258-271.
- 7 Kim DY, Jo J, Joe SG, Kim JG, Yoon YH, Lee JY. Comparison of visual prognosis and clinical features of cytomegalovirus retinitis in HIV and non-HIV patients. *Retina* 2017;37(2):376-381.
- 8 Ye JJ, Li HY, Sun D, Min HY, Han BL, Hu TS. Cytomegalovirus retinitis associated with acquired immunodeficiency syndrome. *Zhonghua Yan Ke Za Zhi* 2005;41(9):803-806.
- 9 Jabs DA, Ahuja A, Van Natta ML, Lyon AT, Yeh S, Danis R; Studies of the Ocular Complications of AIDS Research Group. Long-term outcomes of cytomegalovirus retinitis in the era of modern antiretroviral therapy: results from a United States cohort. *Ophthalmology* 2015;122(7):1452-1463.
- 10 Thorne JE, Jabs DA, Kempen JH, Holbrook JT, Nichols C, Meinert CL; Studies of Ocular Complications of AIDS Research Group. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Ophthalmology* 2006;113(8):1432-1440.
- 11 Jabs DA, Ahuja A, Van Natta M, Lyon A, Srivastava S, Gangaputra S; Studies of the Ocular Complications of AIDS Research Group. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: five-year outcomes. *Ophthalmology* 2010;117(11):2152-2161.e1-2.
- 12 AIDS Professional Group, Society of Infectious Diseases, Chinese Medical Association. Third edition of the guidelines for diagnosis and treatment of HIV/AIDS (2015). *Chinese Journal of Clinical Infectious Diseases* 2015;8(5):385-401.
- 13 Fundus Disease Professional Group, Society of Ophthalmology, Chinese Medical Association. Quality control standard for intravitreal injection of medications to treat retinopathy in China. *Chinese Journal of Ophthalmology* 2015;51(12):892-895.

- 14 Lai M, Zhang YL, Tian YK, Hua W, Wu H, Guo C. Understanding of cytomegalovirus disease in Guideline for the Prevention and Treatment of Opportunistic Infection among HIV-infected Adults and Adolescents (2016 version, America). *China Medical Herald* 2017;14(2):37-40.
- 15 Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C, Cooper B, Dubberke ER, Engemann AM, Freifeld AG, Greene JN, Ito JI, Kaul DR, Lustberg ME, Montoya JG, Rolston K, Satyanarayana G, Segal B, Seo SK, Shoham S, Taplitz R, Topal J, Wilson JW, Hoffmann KG, Smith C. Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2016;14(7):882-913.
- 16 Li XX, Zhao JL. Retina. Tianjin Science and Technology Translation Publishing Co., Ltd., 2011: p.1609
- 17 Fan JJ, Tao Y, Hwang DK. Comparison of intravitreal ganciclovir monotherapy and combination with foscarnet as initial therapy for cytomegalovirus retinitis. *Int J Ophthalmol* 2018;11(10):1638-1642.
- 18 Miao H, Tao Y, Jiang YR, Li XX. Multiple intravitreal injections of ganciclovir for cytomegalovirus retinitis after stem-cell transplantation. *Graefes Arch Clin Exp Ophthalmol* 2013;251(7):1829-1833.
- 19 Sampat KM, Garg SJ. Complications of intravitreal injections. *Curr Opin Ophthalmol* 2010;21(3):178-183.
- 20 Bittencourt MG, Agbedia OO, Liu HT, Annam R, Sepah YJ, Leder HA, Sophie R, Ibrahim M, Akhtar A, Akhlaq A, Do DV, Nguyen QD. Ocular complications of HIV/AIDS in the era of HAART. *Expert Rev Ophthalmol* 2012;7(6):555-564.