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

Lian-Yong Xie, Chao Chen, Wen-Jun Kong, Kui-Fang Du, Chun-Gang Guo, Hong-Wei Dong, Wen-Bin Wei

1Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China
2Beijing Tongren Eye Center, Beijing Key Laboratory of Intraocular Tumor Diagnosis and Treatment, Beijing Ophthalmology & Visual Sciences Key Lab, Beijing Tong Ren Hospital, Capital Medical University, Beijing 100730, China

Correspondence to: Wen-Bin Wei. Beijing Tongren Eye Center, Beijing key Laboratory of Intraocular Tumor Diagnosis and Treatment, Beijing Ophthalmology & Visual Sciences Key Lab, Beijing Tong Ren Hospital, Capital Medical University, Beijing 100730, China. weiwenbintr@163.com

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

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/μL 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.
Individualized therapy of CMVR in AIDS

General Information A total of 32 eyes in 23 AIDS patients [20 males and 3 females, with a mean age of 34.78±7.19y (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/μL.

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) 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 antiretroviral 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 cure 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 >1500 μm and peripheral lesions at a distance 1500 μm[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.
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 without 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).

REFERENCES


16 Li XX, Zhao JL. Retina. Tianjin Science and Technology Translation Publishing Co., Ltd., 2011: p.1609


