Continued Decline of Aqueous Interleukin-8 After Multiple Intravitreal Injections of Ganciclovir for Cytomegalovirus Retinitis

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Abstract

Purpose: To evaluate the relationship between aqueous inflammation cytokines and cytomegalovirus (CMV) particles in patients with cytomegalovirus retinitis (CMVR), and evaluate the changes in aqueous inflammation cytokines during multiple intravitreal injections of antiviral drugs for CMVR.

Methods: There were 10 patients (12 eyes; 16 courses of treatment per eye) who underwent continued intravitreal ganciclovir or foscarnet for treatment of CMVR. Before each intravitreal injection, 50–100 μ L of aqueous humor was removed and sent to the laboratory to examine the concentration of the CMV DNA load by using polymerase chain reaction and to examine the concentration of interleukin (IL)-1 β , IL-6, IL-8, IL-10, tumor necrosis factor (TNF)- α , and IL-12p70 using a cytometric bead array.

Results: A Kendall correlation test showed that the concentration of the CMV DNA load in the aqueous humor was significantly associated with the aqueous level of IL-6 ($P < 0.001$, $r = 0.327$) and IL-8 ($P < 0.001$, $r = 0.381$), but not significantly associated with IL-1 β , IL-10, IL-12p70, and TNF- α . The boxplots showed that the concentration of the aqueous CMV DNA load, IL-8 and IL-10 continuously declined after multiple intravitreal injections of antiviral drugs, and the decline trend of IL-8 was most remarkable. IL-1 β , IL-10, TNF- α , and IL-12p70 were negative in some of the aqueous levels of CMVR patients throughout the course of treatment (25.0%–62.5%).

Conclusions: Our study showed that IL-8 was significantly associated with the aqueous level of CMV copies and continuously declined during a course of treatment that involved multiple intravitreal injections of antiviral drugs. IL-8 may be considered a good quantitative laboratory indicator of the recovery of CMVR.

Introduction

CYTOMEGALOVIRUS RETINITIS (CMVR) is a leading cause of blindness in patients who are immunosuppressed due to acquired immunodeficiency syndrome (AIDS), chemotherapy, corticosteroid therapy, or malignancy, and in newborns who are congenitally infected.^{1–5} In China, the prevalence of CMVR in hospitalized AIDS patients is 7.6%.⁶

Once CMVR is diagnosed, anti-cytomegalovirus (CMV) therapy should be administered.⁷ Multiple intravitreal injections of ganciclovir or foscarnet appeared to be well tolerated and improvement of the retinitis was observed,

either in AIDS patients^{8,9} or in non-AIDS patients.^{4,10} Previous studies implied that inflammation cytokines, including interleukin (IL)-2,^{11–14} IL-4,¹⁵ and IL-17,¹⁶ may be involved in the development of CMVR by influencing the patient's susceptibility to it. However, to our knowledge, these previous studies about the relationship between inflammation cytokines and CMVR are generally based on animal or cell studies. Furthermore, how the intraocular inflammation cytokines change after intravitreal injections of antiviral drugs remains unknown. Therefore, in this report, we will focus on the changes in the aqueous level of inflammation cytokines, including IL-1 β , IL-6, IL-8, IL-10, the tumor necrosis factor

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(TNF)- α , IL-12p70, and the concentration of CMV DNA load in the aqueous humor after multiple intravitreal injections of ganciclovir or foscarnet.

Methods

This clinical interventional retrospective case-series study included 10 consecutive patients (12 eyes) with CMVR. Initially, 4 intravitreal injections of ganciclovir (Likewei; Hubei Keyi Pharmaceutical Co., Ltd, Wuhan, China) were given without systemic use of antiviral drugs. The interval was 1 week between injections, and the dosage of ganciclovir varied. It was 6.0 mg for the first injection, 4.5 mg for the second injection, and 3.0 mg for the third and fourth injections. If the CMV DNA load was still positive ($>1,000$ copies/mL) after 4 injections, then further intravitreal injections of ganciclovir (always 3.0 mg) were given. Then, the patients were given a routine exam. In 4 eyes, recurrent CMVR with enhanced retinal hemorrhage and exudates and an increased CMV DNA load in the aqueous humor were observed, and multiple intravitreal injections of foscarnet were then given until the CMV DNA load came back negative or the patient stopped coming in for follow-up visits. Based on our previous experience that the level of inflammation cytokines in aqueous humor of senile cataract was generally below detectable threshold, normal control was not included in the present study.

Use of the off-label drug and its potential risks and benefits were discussed in detail with all patients, and formal written consent was obtained. The treatment regimen and dosage of intravitreal ganciclovir were based on the following comprehensive understanding: (1) several clinical studies have used high doses of intravitreal injections of ganciclovir.^{17–19} It has been reported that a high-dose intravitreal ganciclovir injection provides a prolonged therapeutic intraocular concentration²⁰; (2) systemic use of ganciclovir would not be considered due to the inhibition of bone marrow in the patients who underwent transplantation of hematopoietic stem cells. The treatment outcome was, therefore, totally dependent on the effect of topical anti-viral drugs; (3) our experience with the unsatisfactory results of low-dosage intravitreal ganciclovir for CMVR patients. The treatment regimen was approved by the institutional review board of our hospital.

The 1 patient who had AIDS accepted highly active antiretroviral therapy after the diagnosis of CMVR.

The injection method was described in detail in previous reports.⁴ Topical anesthesia was applied before the injection, and the patients were draped completely as for any intraocular surgery. A lid speculum was inserted, and more than 50–100 μ L of aqueous humor was obtained by paracentesis using a sharp 27-gauge needle. Next, ganciclovir was injected in the inferotemporal region using a 27-gauge needle trans-conjunctivally at 3–3.5 mm from the limbus. An antibiotic ointment (ofloxacin) was applied after the injection.

The aqueous humor sample from each eye was separated into 2 parts to measure the level of CMV virus particles and inflammation cytokines. A real-time polymerase chain reaction (PCR) was applied to immediately detect the amount of CMV DNA load in the samples.

For the CMV test, DNA was extracted from the aqueous humor using the Liferiver CMV Real-Time PCR Kit. For

each aqueous humor, 12,000 rpm for 10 min, discarding supernatant cell and virus-lysis were performed by 99°C incubation for 10 min of the samples in 50 μ L nucleic acid extraction liquid. DNA was enriched in the supernatant by 13,000 rpm for 10 min. These extracted DNA samples were used for quantitative PCR.

Liferiver CMV Real-Time PCR Kit Mix contains reagents and enzymes for the specific amplification of immediate early gene region of the HCMV-DNA. A standard curve was obtained from the quantitation standard CMV DNA positive controls provided by the manufacturer. For the PCR amplification, 4 μ L of the DNA sample was added to 36 μ L of the working master mix. The amplicons were then detected by measuring fluorescence, using the Roche LightCycle[®] 480 real-time PCR system with the following amplification conditions: 37°C for 2 min, 94°C for 2 min, followed by 40 cycles of 93°C for 15 s and 60°C for 1 min. The linear range of the CMV DNA test was from 5×10^4 to 5×10^7 copies/mL. Quantitative results were reported if $>1 \times 10^3$ copies/mL.

The concentrations of IL-1 β , IL-6, IL-8, IL-10, IL-12p70, and TNF- α were measured by applying a cytometric bead array (No. 552932; BD Bioscience, San Jose, CA) with flow cytometry (BD FACSCalibur; BD Bioscience).²¹

Statistical analysis was done using a commercially available statistical software package (SPSS for Windows, version 20.0; IBM-SPSS, Chicago, IL). The normality of data was tested by the Shapiro–Wilk test. The Shapiro–Wilk test showed that the aqueous concentration of CMV DNA load and inflammation cytokines did not fit the normal distribution. The Kendall and Spearman correlation test was then used to explore the relationship between the aqueous level of each cytokine and the amount of CMV DNA load. By using boxplots, the mean loads of CMV and inflammation cytokines were compared against the times of injection, and the trend of which changed with time were judged from it. All *P*-values were 2-sided and were considered statistically significant if <0.05 .

Results

The study group included 10 patients (6 female, 60.0%; 12 eyes) with a mean age of 37.9 ± 15.9 years, ranging from 14 to 72, with a median age of 36.5 years. CMVR was secondary to hematopoietic stem cell transplantation in 8 patients, AIDS in 1 patient, and thymectomy in 1 patient. The duration of visual symptoms from onset varied from 1 week to 1 month (mean: 2.6 ± 1.2 weeks).

CMVR recurred in 4 eyes, prompting a change in the intravitreal injection from ganciclovir to foscarnet (as mentioned earlier). There were 16 groups of measurement data from aqueous humor samples, which included 12 groups whose primary treatment was ganciclovir and 4 groups whose secondary treatment was foscarnet (Table 1).

The Kendall correlation test showed that the concentration of CMV DNA load in the aqueous humor was significantly associated with the aqueous level of IL-6 ($P < 0.001$, $r = 0.327$) and IL-8 ($P < 0.001$, $r = 0.381$), but not significantly associated with IL-1 β ($P = 0.783$, $r = -0.027$), IL-10 ($P = 0.097$, $r = 0.153$), IL-12p70 ($P = 0.531$, $r = 0.064$), and TNF- α ($P = 0.947$, $r = 0.007$). Similarly, the Spearman correlation test showed that the concentration of CMV DNA load in the aqueous humor was significantly associated with

the aqueous level of IL-6 ($P < 0.001$, $r = 0.542$) and IL-8 ($P < 0.001$, $r = 0.472$), but not significantly associated with IL-1 β ($P = 0.785$, $r = -0.035$), IL-10 ($P = 0.116$, $r = 0.202$), IL-12p70 ($P = 0.534$, $r = 0.080$), and TNF- α ($P = 0.958$, $r = 0.007$).

The boxplots showed that the concentration of the aqueous CMV DNA load, IL-8, and IL-10 continuously declined after multiple intravitreal injections of antiviral drugs (Fig. 1). The decline trend of IL-8 was most remarkable. With regard to IL-10, it was negative throughout the entire course of treatment in 4 groups of data (25.0%), including data from before the first injection when the CMVR was active. The IL-8 was only negative twice after 2 intravitreal injections of ganciclovir in 1 group of data. In addition, the IL-1 β was negative throughout the entire course of treatment in 6 groups of data (37.5%) and was negative before initial treatment in another 3 groups of data. The TNF- α was negative throughout the entire course of treatment in 12 groups of data (75.0%) and was negative before initial treatment in another 3 groups of data, that is, it was only positive from baseline in 1 group of data. The IL-12p70 was

negative throughout the entire course of treatment in 10 groups of data (62.5%) and was negative before initial treatment in another 3 groups of data, that is, it was only positive from baseline in 3 groups of data. Figure 2 showed the pre- and post-treatment fundus photographs and corresponding CMV DNA load and concentrations of IL-1 β , IL-6, IL-8, IL-10, IL-12p70, and TNF- α in one of the cases.

Discussion

Based on the PCR technique, the measurement of pathogens in the vitreous or aqueous humor, that is, CMV, has been widely accepted for diagnosis of CMVR throughout the world.²²⁻²⁵ Due to the multiple circles of amplifications, PCR offers advantages in detecting traces of DNA, but fails to be a good quantitative indicator for accurately showing the active degree of CMVR.

The results of our study clearly showed that the aqueous level of IL-8 was significantly associated with the aqueous level CMV DNA load, and that it continuously declined during the course of treatment with multiple intravitreal

FIG. 1. Boxplots showing the changes in concentration of interleukin (IL)-1 β , IL-6, IL-8, IL-10, tumor necrosis factor (TNF)- α , IL-12p70, and cytomegalovirus particles in the aqueous humor during multiple intravitreal injections of antiviral drugs for treatment of cytomegalovirus retinitis.

FIG. 2. The pre- and post-treatment fundus photographs of 1 subject who underwent 4 intravitreal injections of ganciclovir with an interval of 1 week. Before each injection, aqueous humor was removed for measurement of inflammation cytokines, including IL-1 β , IL-6, IL-8, IL-10, TNF- α , IL-12p70, and cytomegalovirus particles. (A) Pre-treatment; (B) at 1 week after second intravitreal injection of ganciclovir; (C) at 1 week after fourth intravitreal injection of ganciclovir; and (D) at 2 months after fourth intravitreal injection of ganciclovir.

IVG	IL-1 β (pg/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)	IL-10 (pg/ml)	IL-12p70 (pg/ml)	TNF- α (pg/ml)	CMV particles (copies/ml)
1	0	193.44	112.31	23.36	0	0	178000
2	0	260.58	96.88	12.09	1.72	1.58	9120
3	1.99	95.48	57.00	4.44	0	0	1030
4	0	99.17	29.25	1.44	0	0	0

injections of antiviral drugs, with accompanying fundus improvement, that is, the decreasing retinal hemorrhage and exudates. Despite the fact that the aqueous level of IL-6 was also significantly related to the aqueous level of CMV DNA load, it did not show a continuous change during the course of treatment. Since the intraocular IL-1 β , IL-10, IL-12p70, and TNF- α can be negative initially in many CMVR eyes, they were not accurate laboratory indicators for showing the degree of inflammation of CMVR.

IL-8 is resistant to temperature and proteolysis and is relatively resistant to acidic environments. These biochemical characteristics make it an ideal molecular candidate for sites of acute inflammation, where it should withstand harsh and hostile conditions.²⁶ These characteristics also make it an ideal laboratory quantitative marker for intraocular inflammation, because it takes time to transfer and examine the intraocular fluid after it is removed during surgery.

TABLE 1. CLINICAL INFORMATION OF PATIENTS WITH CYTOMEGALOVIRUS RETINITIS IN THIS STUDY

No.	Eye	CMVR	Systemic status	Initial aqueous CMV (copies/mL)	Treatment
111	Right	Primary	HSCT	44,200	4 IVGs
115	Right	Primary	Post-thymectomy	1,510,000	4 IVGs
115	Right	Recurrent	Post-thymectomy	99,200	5 IVFs
138	Left	Primary	HSCT	256,000	4 IVGs
138	Left	Recurrent	HSCT	822,000	4 IVFs
138	Right	Primary	HSCT	254,000	5 IVGs
142	Left	Primary	HSCT	488,000	5 IVGs
175	Left	Primary	HSCT	178,000	4 IVGs
175	Right	Primary	HSCT	435,000	3 IVGs
178	Left	Primary	HSCT	8,160	4 IVGs
194	Right	Primary	AIDS	1,870,000	4 IVGs
194	Right	Recurrent	AIDS	12,900	3 IVPs
198	Right	Primary	HSCT	23,200	4 IVGs
198	Right	Recurrent	HSCT	8,420	3 IVFs
217	Left	Primary	HSCT	10,800	3 IVGs
228	Left	Primary	HSCT	69,600	3 IVGs

AIDS, acquired immune deficiency syndrome; CMV, cytomegalovirus; CMVR, cytomegalovirus retinitis; HSCT, hematopoietic stem cell transplantation; IVF, intravitreal injection of foscarnet; IVG, intravitreal injection of ganciclovir.

The principal cellular sources of IL-8 are typically monocytes and macrophages,²⁷ and the addition of H₂O₂ caused a dose-dependent stimulation of IL-8 release.²⁶ IL-8 bears the primary responsibility for the recruitment of monocytes and neutrophils, the signature cells of acute inflammatory response.²⁸ Cellular recruitment occurs through the development of a chemotactic gradient, which causes the inflammatory cell to move toward an area of increased chemokine concentration. This gradient aids in bringing cells toward the site of inflammation and also retains them once they have arrived.²⁹ In addition to the inflammatory diseases, IL-8 has diagnostic and prognostic values for malignant tumors.^{30,31} IL-8 affects proliferation and migration of cancer cells, tumor angiogenesis, and metastasis. Elevated concentrations of IL-8 are indicative of malignant processes in cerebrospinal fluid, urine, saliva, interstitial fluid, and cervicovaginal secretions.^{30,32} Higher IL-8 levels are typically found in high-grade peritumoral fluids rather than in low-grade tumors and benign conditions, with the exception of inflammatory processes.³⁰

In the current study, the aqueous level of IL-10 was not significantly associated with the aqueous level of CMV, nor did it show continuous changes as fundus improved during multiple intravitreal injections of anti-virus treatments. Our findings were consistent with Blalock et al.'s study.³³ They found that murine CMV-infected eyes of IL-10^{-/-} mice with murine AIDS of 8 weeks duration exhibited retinitis and infectious virus equivalent to that observed in murine CMV-infected eyes of wild-type mice with murine AIDS. Similar results were also observed in IL-4^{-/-} mice. Therefore, one may conclude that IL-10 alone neither plays a role in increased susceptibility to CMVR nor is significantly influenced by anti-virus treatment.

There were pros and cons to this study. To our knowledge, this is the first study that continuously follows the changes of inflammation cytokines during multiple intravitreal injections of antiviral drugs for CMVR, and also the first study which evaluates the relationship between inflammation cytokines and CMV particle concentration in human samples. However, the small number of participants (16 CMVR eyes) limited the impact of this study. Moreover, only 6 inflammation cytokines were selected, and a recent study showed that the levels of other cytokines in the aqueous humor, including IP-10, fractalkine, PDGF-AA, G-CSF, Flt-3L, and MCP-1, varied significantly among HIV with or without CMVR groups.³⁴ Furthermore, the quantitative results of CMV were reported if $> 1 \times 10^3$ copies/mL for the kit used in this study, which is less sensitive than most accepted quantitative PCR kits for CMV that usually range 10–100 copies/mL. In addition, the systemic diseases of these CMVR patients were not the same, and blood CD4⁺ T cell count was not performed, which may be drawbacks. However, considering that CMVR secondary to varied systemic diseases shared the same pathogen, and considering that the intraocular environment is relatively independent, the influence may not be significant enough to affect the conclusion of this study.

In summary, our study showed that IL-8 was significantly associated with the aqueous level of CMV copies and continuously declined during multiple intravitreal injections of antiviral drugs (it was accompanied by improved fundus appearance). IL-8 may be considered a good quantitative laboratory indicator of the recovery of CMVR.

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Author Disclosure Statement

No competing financial interests exist.

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