The High-Dose, Alternate-Week Intravitreal Ganciclovir Injections for Cytomegalovirus Retinitis in Acquired Immune Deficiency Syndrome Patients on Highly Active Antiretroviral Therapy

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Objectives: *To evaluate the efficacy, and complications of the high-dose, alternate-week, intravitreal ganciclovir injection for cytomegaloviral retinitis (CMVR) in acquired immune deficiency syndrome (AIDS) patients on highly active antiretroviral therapy (HAART).*
Design: *Retrospective case series.*
Participants: *AIDS patients with CMVR and on HAART.*
Material and Method: *The high-dose, 4 mg/0.1 ml, ganciclovir was injected intravitreally to the enrolled patients on an alternate-week basis. The patients were monitored clinically until the retinitis was inactive, then the injections were withdrawn. The injections were re-initiated if relapse occurred.*
Main Outcome Measures: *The number of eyes achieved inactive retinitis and corresponded to the number of injections, number of relapses and corresponded duration, visual acuity during the injection, and complications of the injection.*
Results: *Inactive lesions were found in 42/51 eyes (82.4%), the corresponding mean number of injections was 5.4 (1-18) per eye. There was no relapse and the corresponded duration of follow-up was 5.1 months (1-16). The final visual outcomes were improved or stable in 26 eyes (50.9%). These visual outcomes were statistically related to initial visual acuity ($p = 0.022$) but not statistically related to the number of injections ($p = 0.929$). Complications were found in 7/51 eyes (13.7%). They were vitreous haze, immune recovery uveitis, rhegmatogenous retinal detatchment, and infectious endophthalmitis.*
Conclusion: *The high-dose, alternate-week, intravitreal injection of ganciclovir may be an alternative for the treatment of CMVR in AIDS patients who are on HAART. However, the induction course is longer than the weekly regimen and close monitoring of patients is essential.*

Keywords: *CMVR, HAART, AIDS, Intravitreal ganciclovir, Ganciclovir*

J Med Assoc Thai 2005; 88 (Suppl 9): S63-8
Full text. e-Journal: *http://www.medassocthai.org/journal*

Cytomegalovirus retinitis (CMVR) is the most common sight threatening complication of acquired immune deficiency syndrome (AIDS). It is also the most common manifestation of CMV diseases[1,2] and occurred in up to 20-40% of HIV positive patients[3,4].

Because CMVR is the ocular manifestation of systemic infection, therefore, the management of CMVR should include both systemic and local treatments[5,6]. Systemic treatments include intravenous gancicolvir, foscanet, and cidofovir for induction and maintenance, and oral ganciclovir for maintenance[7]. Local treatments include intravitreal ganciclovir, foscanet, ganciclovir implant[8] and also intravitreal fomivirsen[9]. Problems associated with the systemic treatments are intolerance of side effects, prolonged courses, poor compliance, high consumption of medical personnel and high-cost devices[10]. On the other hand, the local treatments have

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fewer side effects, and consume less time and cost[11]. The major drawback of local treatment alone is relapse of the retinitis[12].

The introduction of highly active antiretroviral therapy (HAART) for AIDS has changed the prognosis of CMVR for the better[13]. The recovery of immunity in patients on HAART can halt the retinitis without any maintenance therapy[14]. The incidence of CMVR has also decreased significantly in these patients. Therefore, the local treatment regimen for CMVR may be modified according to the immune status of AIDS patients who are on HAART.

The present study was conducted to evaluate the efficacy of the high-dose intravitreal ganciclovir injection, 4 mg in 0.1 ml[15-17], which was extended from weekly to alternate-week application. The monitoring of the retinitis was performed on the basis of clinical examination only. This regimen may be useful for patients with low socioeconomic status who cannot afford the regular weekly injection, and in a CMVR clinic which is attended by too many patients. Side effects and complications of this modified regimen were also observed.

Material and Method

The present study was conducted by a retrospective review of medical records of acquired immunodeficiency syndrome (AIDS) patients who underwent intravitreal injection of ganciclovir for CMVR in the Retina Clinic, Department of Ophthalmology, Rajavithi Hospital between May 2002 and July 2005. The patients were included in the study if they were already on HAART or received HAART after the first injection, and had no previous treatment for CMVR. They were excluded if they had other concurrent retinal diseases such as retinal detachment at the first visit. The patients who did not accept intravitreal injection modality, and those lost to follow-up after the first injection were also excluded.

The CMVR was diagnosed clinically by dilated fundus examination using indirect ophthalmoscopy, when the characteristic appearance of fluffy retinal opacification associated with hemorrhage and vascular sheathing were presented[6]. All CMVR included in the present study had zone I disease. It was defined as the retinitis which was confined to an area within 1,500 μm of the edge of the optic nerve or 3,000 μm of the center of the fovea[18].

All CMVR were treated as soon as the time of diagnosis and then monitored every 2 weeks by Snellen visual acuity (VA), dilated fundus examination using indirect ophthalmoscopy, and slit-lamp biomicroscopy if necessary. All patients gave informed consent before the initiation of treatment. The course of follow-up was made until the lesions were inactive[6] without CD4 counts monitoring. The inactive lesions combined several features including loss of satellite lesions, disappearance of venous sheathing, stable border, color change from white to grey or yellow, translucent retinal scar, and mottling of retinal pigment epithelium[6].

If the lesions were inactive, the injections were withdrawn. The patients were then monitored every 2 weeks for 1 month, and every month for 2 months. If relapse did not occur after the withdrawal for 6 months, they would be monitored every 2 months. Whenever relapse occurred during the course of follow-up, the re-injections with the same dosage and interval were initiated.

In the injection procedure, the eyes were anesthetized with 4% tetracaine, and instilled with topical antibiotics. The injection of 4 mg/0.1ml ganciclovir was given via 30-gauge needles through pars plana at 3.5 mm or 4.0 mm from limbus depended on phakic status of the patients. The injection could be made at any quardrant except at the 3 and 9 o'clock. Immediately after the injection, an antibiotics-soaked cotton tip was pressed at the pars plana wound to prevent vitreous reflux and stop bleeding. Anterior chamber paracentesis was then performed for keeping good intraocular pressure in most patients. Finally, antibiotics eye drops were re-instilled to the eyes.

Results

During the study period, there were 70 eyes (42 patients) of CMVR which under went the intravitreal ganciclovir injection. A total of 10 eyes were then excluded because the patients did not receive HAART either at the first presentation or after the first injection. Of 60 eyes of CMVR on HAART, an eye of a patient developed rhegmatogenous retinal detachment at the first visit, another eye had no light perception, and 7 eyes received only one injection without additional follow-up; all these cases were also excluded. The clinical characteristics of the enrolled cases (51 eyes of 33 patients) were shown in Table 1.

Table 2 demonstrates fundscopic outcomes of the enrolled patients. Inactive lesions were seen in 42 of 51 eyes (82.4%). The total number of injections in these eyes was 227, thus the average number of injections per eye with inactive lesions was 5.4. Of all these 42 eyes, 34 eyes could be monitored with the mean duration of 5.1months after the withdrawal of injection.

Table 1. Clinical characteristics of the patients with cytomegalovirus retinitis

Number of patients	33
Number of eyes	51
Male	13
Female	20
Mean age in years (range)	33.3 (20-51)
Number of patients on HAART at first presentation (%)	5 (15%)
Number of patients on HAART after the first injection (%)	28 (85%)
Associated diseases	
Brain toxoplasmosis	1
Pulmonary tuberculosis	1
Dissiminated tuberculosis	1

Table 2. Outcomes of the patients treated wih the high-dose, alternate-week intravitreal ganciclovir injection

• Inactive retinitis (eyes)	42
Mean numbers of injection until inactive per eyes (range)	5.4 (1-18)
Mean duration of treatment until inactive (range) (weeks)	11.8 (2-36)
• Relapse of retinitis (eyes)	0
Mean duration of follow-up after withdrawal of treatment in months (range)	5.1 (1-16)
• Active retinitis (eyes)	2
Numbers of injection of the first case	13
Numbers of injection of the second case	9

All of these eyes were still inactive at the final visit. Only one patient had relapsed disease after the injections were withdrawn from both eyes for one month; the injection was then re-introduced until the retinitis in each eye was inactive. Both eyes were monitored again and the relapse was not found at two-months after the new withdrawal. There were only 2 eyes in which the retinitis were still active at the end of the present study. The numbers of injections in these eyes were 13 and 9 respectively.

Table 3 demonstrates visual outcomes of the enrolled patients. It was found that 50.9% of these eyes could have improved or stabilized visual acuity. It was then demonstrated that the final visual outcomes were statistically related to initial visual acuity ($p = 0.022$). On the other hand, the outcomes were not statistically related to the number of injections ($p = 0.929$).

The complications of the injection and the number of injections in those cases are demonstrated in Table 4.

Discussion

One of the major problems in treatments of CMVR in Thailand is the low socioeconomic status of the patients. Some patients cannot afford to have standard intravenous therapy, long-term oral therapy, or even weekly intravitreal injections. The alternate-week injection regimen in the present study seems to be well accepted with only 6 patients (7 eyes) excluded due to lost follow-up. The average duration of follow-up in all enrolled patients was 5.1 months. The alternate-week regimen was also effective in causing resolution of CMVR. However, the induction of resolution period was longer than the biweekly and weekly regimens. This may suggest that the intravitreal concentrations of ganciclovir in this alternate-week regimen cannot effectively cover the 2-week interval of injections but the disease can be stabilized by the recovered immunity in patients on HAART. The recovered immune system may also cause no relapse in all patients whose injections were withdrawn after complete resolution. Although the follow-up period after the withdrawal may not be long enough in the present study, the average 5-month duration without relapse is already longer than the time to relapse for the intravenous ganciclovir regimen. Furthermore, there were 10 eyes which could be monitored for more than 8 months, the time to relapse for the ganciclovir implant.

Final visual outcomes of the ganciclovir injection in the present study are related to initial visual acuity which implies the degree of mucular involvement before treatments. The only 50% improved or stable vision was achieved despite the 82.4% (42/51 eyes, Table 2) resolution of the disease may be partially explained by the initial poor visual acuity in almost half of the patients. The high dose, 4 mg/0.1ml, ganciclovir seems to be well tolerated in the present study as suggested by other studies[16-18]. The non-statistical significance of the relationship between final visual outcomes and the number of injections also suggests the safety of the dosage. However, if the immune system of the patients can stabilize CMVR, a standard 2 mg/0.1 ml dosage may be used for this alternate-week regimen. Further studies comparing the 4 mg and 2 mg dosage may be warranted.

A limitation in the present study includes retrospective data collection. A prospective, randomized, controlled trial comparing the standard weekly and this alternate-week regimen may be needed to prove the real efficacy of the latter. The use of CD4 counts combined with fundus examination for monitoring the disease may lessen the number of injections,

Table 3. Visual acuity of the patients treated with the high-dose, alternate-week intravitreal ganciclovir injection

	Improved N (%)	Stable N (%)	Worse N (%)
All eyes (N = 51)	9 (17.6)	17 (33.3)	25 (49)
Subgroup analysis			
Grouped by initial visual acuity [a]	1	13	10
20/20-20/40 (N = 24)	3	1	7
20/50-20/100 (N = 11)	5	2	8
< 20/200 (N = 15)	0	1	0
PL (N = 1)			
Grouped by numbers of injection [b]			
1-6 (N = 35)	7	11	17
7-12 (N = 11)	1	4	6
13-18 (N = 5)	1	2	2

The improved visual outcomes mean visual acuity improvement more than 3 lines of Snellen chart, stable visual outcomes mean change of visual acuity within 3 lines, and worse visual outcomes mean worsening of visual acuity more than 3 lines. Any change of visual acuity from better than or equal to 20/200 to an unability to read any Snellen optotype was also defined as worse visual outcomes.

[a] Statistical significance, Chi-square test, p = 0.022

[b] Not Statistical significance, Chi-square test, p = 0.929

Table 4. Complications of the treatment

	Number of eyes	Number of injections
Vitreous haze	1	15
Immune recovery uveits	2	5, 9
Rhegmatogenous retinal detachment	2	2, 6
Infectious endophthalmitis	2	8, 2

thus lessen the possibilities of side effects and complications.

In summary, the high-dose, 4 mg in 0.1ml, intravitreal ganciclovir injections on an alternate-week basis for CMVR in AIDS patients who are on HAART can cause complete resolution of the disease with less chance of relapse. This regimen of treatment may be an alternative for patients who cannot afford a weekly injection regimen, but the prolonged course of induction to resolution is the major drawback. Close monitoring of the patients is also recommended.

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การรักษาโรคจอประสาทตาอักเสบจากเชื้อ CMV ในผู้ป่วยโรคภูมิคุ้มกันบกพร่อง (AIDS) ซึ่งได้รับยาต้านไวรัส HAART ด้วยวิธีฉีดยา ganciclovir ขนาดสูง สัปดาห์เว้นสัปดาห์ เข้าน้ำวุ้นตา

กนกวรรณ ยุตติธรรม, ไพศาล ร่วมวิบูลย์สุข

วัตถุประสงค์: *เพื่อประเมินถึงประสิทธิภาพและภาวะแทรกซ้อนของการรักษาโรคจอประสาทตาอักเสบจากเชื้อ CMV ในผู้ป่วยโรคภูมิคุ้มกันบกพร่อง (AIDS) ซึ่งได้รับยาต้านไวรัส HAART ด้วยวิธีฉีดยา ganciclovir ขนาดสูง สัปดาห์เว้นสัปดาห์ เข้าน้ำวุ้นตา*

รูปแบบวิธีวิจัย: *การศึกษาผู้ป่วยแบบย้อนหลัง*

ผู้เข้ารับการวิจัย: *ผู้ป่วยโรคภูมิคุ้มกันบกพร่อง (AIDS) ซึ่งได้รับยาต้านไวรัส HAART และเป็นโรคจอประสาทตาอักเสบจากเชื้อ CMV*

วัสดุและวิธีการ: *ผู้ป่วยดังกล่าวได้รับการฉีดยา ganciclovir ขนาดสูง (4 มก.ใน0.1 มล.) เข้าน้ำวุ้นตา ทุกสองสัปดาห์ และได้รับการติดตามผลการฉีดด้วยการตรวจทางคลินิกจนกระทั่งรอยโรคสงบจึงหยุดยา หากมีการเป็นซ้ำจะได้รับการฉีดใหม่*

ตัวชี้วัดหลัก: *จำนวนตาที่รอยโรคสงบ, จำนวนครั้งที่ฉีดจนสงบ, จำนวนตาที่เป็นซ้ำ, ระยะเวลาการติดตามจนเป็นซ้ำ, ค่าความชัดของสายตา, และภาวะแทรกซ้อน*

ผลการศึกษา: *พบรอยโรคสงบใน 42 จาก 51 ตา (82.4%) ด้วยจำนวนการฉีดเฉลี่ย 5.4 (1-18) ครั้งต่อตา ไม่พบจำนวนตาที่เป็นซ้ำจากการติดตามหลังหยุดยาเป็นเวลา 5.1 (1-16) เดือน ค่าความชัดของสายตาในการตรวจครั้งสุดท้ายอยู่ในระดับดีขึ้น หรือคงที่ ใน 26 ตา (50.9%) ค่าความชัดของสายตานี้มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับระดับสายตาก่อนเริ่มรักษา (p = 0.022) แต่ไม่สัมพันธ์กับจำนวนครั้งของการฉีดยา (p = 0.929) ภาวะแทรกซ้อนพบใน 7 ตา (13.7%) ได้แก่ น้ำวุ้นตาขุ่น ม่านตาอักเสบจากภูมิคุ้มกันฟื้นตัว จอประสาทตาฉีกขาดและลอกหลุด และการติดเชื้อในตา*

สรุป: *การฉีดยาตามการศึกษานี้อาจเป็นทางเลือกหนึ่งในการรักษาผู้ป่วย AIDS ซึ่งเป็นโรคจอประสาทตาอักเสบจากเชื้อ CMV และได้รับยาต้านเชื้อไวรัส HAART แต่ระยะเวลาการรักษาจนรอยโรคสงบนานกว่าการฉีดทุกสัปดาห์ และผู้ป่วยควรได้รับการติดตามอย่างใกล้ชิด*