Intravitreal Foscarnet for Cytomegalovirus Retinitis in Patients with AIDS

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To determine the visual outcome, progression, and complications of patients with acquired immunodeficiency syndrome-related cytomegalovirus (CMV) retinitis treated with intravitreal foscarnet (2.4 mg in 0.1 ml per injection), a retrospective study was carried out in 193 patients. Induction therapy consisted of two injections a week until the lesions were inactive. Maintenance therapy consisted of one injection a week until relapse, then re-induction was instituted. In 301 treated eyes, visual acuity remained stable in 184 (61%), improved in 16 (5%), and decreased in 101 (34%). Of these, 15 retinal detachments, 13 intravitreal hemorrhages, 3 endophthalmitis, and 2 cataract occurred. Median time of first progression was 15 weeks. Involvement of the fellow eye occurred in 35% of the patients during treatment of the first eye. Intravitreal foscarnet appeared to be a useful alternative treatment for patients intolerant or unaffordable to intravenous anti-CMV drugs, but the complications of this treatment should also be considered.

Keywords: *Acquired Immunodeficiency Syndrome (AIDS), Cytomegalovirus (CMV), Retinitis, Foscarnet, Intravitreal injection*

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Cytomegalovirus (CMV) retinitis is the most common sight-threatening complication in acquired immune deficiency syndrome (AIDS), occurring in 33% of patients in a Chiang Mai study[1]. Currently, four antiviral agents are effective in the treatment of CMV retinitis: ganciclovir, foscarnet, cidofovir, and fomivirsen[2-5]. Formerly, systemic treatment with ganciclovir and foscarnet was the mainstay of management, but severe side effects often limited their use and this led to their discontinuation[6-15]. Intravitreal therapy of both drugs proved to be effective alternatives in stopping the progression of the disease[16-25].

The authors present a retrospective study of 193 patients treated with intravitreal foscarnet to assess its efficacy as the first choice treatment of CMV retinitis.

Material and Method

A total of 193 AIDS patients with active CMV retinitis who were referred for the intravitreal injection at the CMV retinitis clinic, Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Thailand, between January 1999 and June 2001, were evaluated.

CMV retinitis was diagnosed clinically by the characteristic features of ophthalmoscopic findings[26]. Active lesions consisted of a white fluffy area of necrotizing retinitis with hemorrhage and vascular sheathing, and inactive lesions consisting of atrophic retina with pigment epithelium mottling and attenuated vessels[26].

Retinitis was classified according to location in 3 retinal zones[26,27] as follows: zone 1, the area extending 3,000 microns from the center of the fovea or 1,500 microns from the border of the optic disc; zone 2, the area anterior to zone 1 and extending to the anterior border of the ampullae of the vortex viens; and zone 3, the area extending anterior from zone 2 to the ora serrata.

All patients were monitored at every visit with Snellen visual acuity (VA), non-contact tonometry, biomicroscopy, dilated funduscopy and fundus draw-

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ing. Fundus photography was performed at the initial visit, and at relapse in some cases.

Treatment was delivered on an outpatient basis and intravitreal injections were performed in the special area of the eye clinic. All patients, except those who were allergic to sulfa drugs, received 1 tablet of acetazolamide (250 mg) 1 hour before the first injection, and were instructed to take this drug at a dosage of 1 tablet three times a day on the day of the next injections. Most of the patients did not get the HAART (highly active anti-retroviral therapy) at the time of the study period.

Before injections, the eyes were anesthesized with topical 0.4% oxybuprocaine. Then a lid speculum was used after cleaning the lids with topical 10% povidone-iodine solution, and the conjunctiva was cleaned with 5% povidone-iodine solution.

The injections were performed with a 27-guage needle attached to a tuberculin syringe, containing 0.1 ml of foscarnet 2.4 mg solution, through the pars plana (4 mm from the limbus), with the needle tip directed toward the mid vitreous. The solution was slowly injected before the needle was withdrawn from the eye, and a cotton tip applicator was put on the injection point to avoid reflux. A tobramycin eye drop was applied to the eye before covering it with an eye pad. Then the patients themselves gently massaged the eye for ocular decompression about 15-20 minutes. Patients were instructed to use topical tobramycin 2 days before and after each injection.

The induction regimen consisted of two injections each week until the lesions were inactive. The maintenance regimen consisted of one injection each week continuously until relapse, then the re-induction treatment was instituted.

Relapse was classified clinically by the presence of new lesions, or enlargement of preexisting lesions, or a change in the opacification of lesion borders[27].Time to progression, as a measure of treatment efficacy, was defined by the interval between start of therapy and relapse[26].

Each eye was analyzed separately for visual outcome by comparison of the visual acuity at baseline examination with the visual acuity at the time of the last follow up. Visual outcome of improvement or deterioration was defined as a change of two or more lines on the Snellen chart, and stabilization was defined as no change in visual acuity, or changes of less than two lines, as described previously by Holland and associates[27].

Statistical analysis used product-limit estimates for survival (Kaplan-Meier method). Computations were performed with the statistical program, SPSS for Windows Version 10.0 (SPSS Inc., Chicago, USA).

The study protocol was approved by the research ethics committee of the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (No. 105/2002).

Results

One hundred and ninety-three patients were treated and followed for a mean period of 25.7 weeks (range, 15 to 83 weeks). The baseline ocular characteristics of the patients at their first visit are shown in Table 1. The patients ranged in age from 21 to 74 years (mean 33.8 years). One hundred and two (53%) were male. Retinitis was initially unilateral in 91 patients (47%) and bilateral in 102 (53%). The visual acuity at initial presentation was in the 6/6 to 6/18 range in 138 eyes (47%), < 6/18-3/60 in 65(22%), < 3/60-PL in 69 (23%), and no PL in 23 (8%). At the initial visit, retinitis affected only zone 1 in 27 eyes (9%), zone 2 in 144 (49%), both zone 1 and zone 2 in 106 (36%), zone 2 and zone 3 in 4 (1%), and all three zones in 14 (5%).

Table 2 summarizes the results of intravitreal foscarnet treatment. Bilateral disease occurred in 32 (35%) of 91 patients, who first came with unilateral involvement, between 1 and 59 weeks (mean 2.1 weeks). In total, 301 eyes were injected with intravitreal foscarnet. Of these, at the time of the last follow-up, 184 (61%) had stable vision, 16 (5%) had improved vision, and 101 (34%) had decreased vision. The median time to first progression, as shown in Fig. 1, was 15.0 weeks (95%CI, 10.4-19.6). Complications in 301 treated eyes included 3 with endophthalmitis. Two

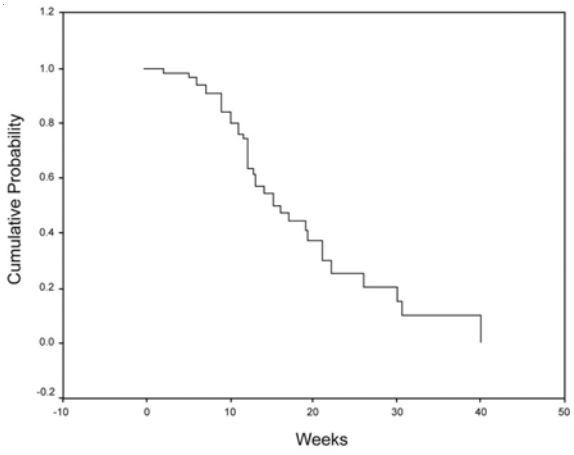

Fig. 1 Kaplan-Meier curve shows probability of time to first progression among patients treated with intravitreal foscarnet

Table 1. Baseline Ocular Characteristics of CMV Retinitis Patients Treated with Intravitreal Foscarnet

Characteristics	No.
No. of patients	193 (100%)
Age (yrs)	
Mean ± SD	33.8±7.1
Range	21-74
Sex	
Male	102 (53%)
Female	91 (47%)
Laterality at first	
Unilateral	91 (47%)
Bilateral	102 (53%)
Visual Acuity at initial visit (eyes)	
6/6-6/18	138 (47%)
<6/18-3/60	65 (22%)
<3/60-PL	69 (23%)
No PL	23 (8%)
Location of lesions at initial visit (eyes)	
Zone 1	27 (9%)
Zone 2	144 (49%)
Zone 1 and zone 2	106 (36%)
Zone 2 and zone 3	4 (1%)
Zone 1 and zone 2 and zone 3	14 (5%)

CMV = Cytomegalovirus

Table 2. Results of Intravitreal Foscarnet Treatment in CMV Retinitis Patients

Results	No.
No. of patients who developed CMV retinitis in the other eye	32 (35%)
Time of developed CMVR in the other eye (wks)	
Mean ± SD	2.1 ± 6.6
Range	1-59
Visual outcome (eyes)	
Stable	184 (61%)
Improved	16 (5%)
Decreased	101 (34%)
Median time to first progression (wks)	15.0 (95%CI, 10.4-19.6)
Complications (eyes)	
Endophthalmitis	3
Retinal detachment	5
Vitreous hemorrhage	13
Cataract	2

CMV = Cytomegalovirus

eyes were treated aggressively with intravitreal antibiotics followed by pars plana vitrectomy, but the outcome was poor. One eye presented late and VA was not preserved. There were 13 eyes with vitreous hemorrhages and 15 with retinal detachment. Two eyes developed cataract during treatment and lens extraction with intra-ocular lens implantation was performed in both eyes and VA was preserved.

Discussion

Although several studies using intravenous treatment with foscarnet have demonstrated success in terms of the initial response rate of CMV retinitis in AIDS patients[4,5,9,10], systemic side effects[11-15] and also the high cost of treatment often limit its use in Thailand. Many studies have shown the efficacy and safety of intravitreal foscarnet in halting the progression of CMV retinitis in AIDS patients[16-19]. The authors therefore evaluated the efficacy of this drug in terms of the visual outcome, progression, and complications of the treatment.

It was known that visual acuity was generally not used as a judgment criterion for the efficacy of treatment because it is dependent on the location and extent of lesions, but preservation of vision is still the goal of therapy. Therefore, the change in visual acuity in terms of visual outcome rather than actual visual acuity measurement was assessed[27]. In the present study, eyes with stabilized, improved, and decreased visual outcome were 61%, 5%, and 34%, respectively. Hence, it is evident that two-thirds of eyes could preserve vision no worse than before by this therapy. However, other factors should also be considered including initial visual acuity, location and extent of lesions, complications of diseases, and other AIDS-related disorders[27].

Median time to first progression in the present study was 15.0 weeks (Table 2 and Fig. 1). In previous studies by the SOCA Research Group, in using this drug intravenously, they were 53 days and 1.3 months[4,5], while it was 4.7 months in another study[28]. In fact, it is difficult to compare these time spans between various studies because of the difference in the baseline characteristics of the patients. Nevertheless, the present study showed that intravitreal foscarnet seemed to be effective in controlling the progression of the disease in the same way as the intravenous route.

Contralateral disease developed in 32 (35%) of 91 patients presenting with uniocular retinitis. Although development of contralateral disease is an expected disadvantage of local therapy, systemic therapy may not offer the expected advantage in this respect, since contralateral retinitis has been reported in 15-68% of patients receiving intravenous therapy[9-15].

There were three eyes with endophthalmitis, representing 1% of 301 treated eyes. Previous series

using intravitreal therapy reported an incidence of endophthalmitis of 0.2% to 0.6% of injections or 4% to 14% of treated eyes[21,22,25]. Serious complications of intravitreal injections, in which multiple injections are required to maintain remission may be the risk factor that attribute to this complication[21,22,25].

The authors had 15 (5%) retinal detachments and 13 (4.3%) vitreous hemorrhages after the onset of intravitreous therapy. These rates are similar to those reported in other intravitreal series (4% to 11% of retinal detachment[20,21,23,25], and 3% of vitreous hemorrhage[23]). The retinal detachment seemed to be attributed to microbreakes located in the porous junction of normal and atrophic retina rather than the complications of this technique, since it occurred in 11% to 24% of CMV retinitis patients with the risk of increasing retinal area involvement and retinal activity[29]. Furthermore, one study reported that intravitreal therapy offered a significant advantage over systemic therapy in the risk of CMV-related retinal detachment[30]. The details of these complications including the management and results are not discussed here, since there are many factors that are not concerned with the objective of the present paper.

Two eyes had cataract, and neither of them had evidence of trauma to the lens capsule that could be associated with intravitreal injections. Many papers have reported that cataract was a rare complication of this technique[16-25].

In conclusion, intravitreal foscarnet is a worthwhile therapeutic alternative for CMV retinitis in AIDS patients who are unable to tolerate or afford systemic antiviral therapy, which is known to be useful in stopping the progression of CMV infection in other organs[11,12]. Although many of these patients have already accepted their fatal disease, their fear of blindness is more significant than their fear of death. However, ophthalmologists using this therapy should bear in mind that multiple injections may be required to maintain remission in many patients, and that serious complications of intravitreal injections may occur.

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การรักษาจอประสาทตาอักเสบจากไซโตเมกะโลไวรัสในผู้ป่วยเอดส์ โดยการฉีดฟอสคาร์เนท เข้าวุ้นตา

สมสงวน อัษญคุณ, โสภา วัฒนานิกร, สุภพ งามทิพากร, จีระเดช ประสิทธิศิลป์

ได้ทำการศึกษาแบบย้อนหลังในผู้ป่วย 193 คน ถึงผลของการมองเห็น การลุกลามของโรค และภาวะแทรกซ้อนในการรักษาโรคจอประสาทตาอักเสบจากไซโตเมกะโลไวรัส ในผู้ป่วยกลุ่มอาการภูมิคุ้มกันบกพร่อง ด้วยการฉีดยาฟอสคาร์เนทเข้าวุ้นตา โดยในระยะเริ่มต้นทำการฉีดครั้งละ 2.4 มิลลิกรัม จำนวน 0.1 มิลลิลิตร สัปดาห์ละ 2 ครั้ง จนรอยโรคสงบ แล้วตามด้วยการฉีดสัปดาห์ละครั้งไปตลอด จนรอยโรคลุกลามใหม่ก็จะเริ่มต้นใหม่ ผลการศึกษาพบว่าตาที่ได้รับการรักษา 301 ตา มีสภาพการมองเห็นเมื่อสิ้นสุดการรักษา (ระยะเวลาเฉลี่ย 25.7 สัปดาห์) ดังนี้ สภาพการมองเห็นเท่าเดิม 184 ตา(61%) สภาพการมองเห็นดีขึ้น 16 ตา (5%) และสภาพการมองเห็นลดลง 101 ตา (34%) ภาวะแทรกซ้อนที่พบคือจอภาพตาหลุด 15 ตา เลือดออกในน้ำวุ้นตา 13 ตา การอักเสบในลูกตา 3 ตา และต้อกระจก 2 ตา การลุกลามของโรคมีระยะเวลาเฉลี่ย 15 สัปดาห์ และผู้ป่วย 35% เกิดรอยโรคในตาอีกข้างหนึ่งในระหว่างการรักษาตาข้างแรก การรักษาด้วยการฉีดยาฟอสคาร์เนทเข้าวุ้นตาเป็นอีกทางเลือกหนึ่งในผู้ป่วยที่ไม่สามารถให้ยาต้านเชื้อไซโตเมกะโลไวรัสทางเส้นเลือดได้ แต่ผลแทรกซ้อนจากการฉีดยาเข้าวุ้นตาเป็นสิ่งที่ต้องคำนึงในการรักษาด้วย