Treatment of Cytomegalovirus Retinitis in AIDS Patients with Intravitreal Ganciclovir

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Background: *Cytomegalovirus (CMV) retinitis is the most common opportunistic ocular infection in AIDS patients, and frequently leads to blindness if untreated. Intravitreal ganciclovir proved to be effective in stopping the progression of the disease.*
Objectives: *To determine the efficacy and complications of intravitreal ganciclovir (2 mg in 0.1 ml per injection) to control CMV retinitis.*
Study design: *A retrospective non-randomized interventional case series.*
Material and Method: *The participants were 363 consecutive patients with CMV retinitis treated at the CMV Retinitis Clinic, Maharaj Nakorn Chiang Mai Hospital over the period from June 2001 to December 2003.The affected eyes received weekly intravitreal injections of 2 mg of ganciclovir until the lesions were inactive, then 2-4 weeks each time continuously or until relapse. If the lesions relapsed, then the weekly schedule was re-started.*
Results: *In 568 treated eyes at the time of last follow up, visual acuity remained stable in 343 (60 %), improved in 76(13 %), and decreased in 149 (26 %). Of these, 33 retinal detachments, 6 intravitreal hemorrhages, 6 endophthalmitis, and 2 cataract occurred. Bilateral disease occurred in 22% of patients who first came with unilateral involvement.*
Conclusion: *Intravitreal ganciclovir appeared to be a worthwhile therapeutic alternative for CMV retinitis patients with unaffordable or intolerant to systemic anti-CMV therapy, but the complications of intravitreal injections should also be recognized.*

Keywords: *Acquired immunodeficiency syndrome (AIDS), Cytomegalovirus (CMV), Retinitis, Ganciclovir, Intravitreal injection*

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Ganciclovir is one of the antiviral agents approved by the United States Food and Drug Administration for the treatment of cytomegalovirus (CMV) retinitis[1-8]. Systemic long-term maintenance administration of this drug is frequently complicated by myelosuppression and neutropenia, that often require attenuation or discontinuation of treatment[5-6,9-10]. In such cases, intravitreal ganciclovir was shown to be locally effective in halting CMV retinitis progression[11-16].

The authors now review a retrospective study of 363 AIDS patients with CMV retinitis treated with intravitreal ganciclovir to assess the efficacy of treatment in terms of visual outcome and complications of treatments.

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Material and Method

A total of 363 AIDS patients with newly diagnosed active CMV retinitis were recruited at the CMV Retinitis Clinic, Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Thailand, from June 2001 through December 2003.

Active CMV retinitis was diagnosed clinically by the characteristic features of retinal whitening, with or without hemorrhage, and vascular sheathing[17]. Inactive lesions consisted of atrophic retina with pigment epithelium mottling and attenuated vessels[17].

Area of retinitis was classified according to location as 3 retinal zones as previously described[4,17,18]. Relapse was classified clinically by the presence of new lesions, or enlargement of preexisting lesions, or a change in the opacification of lesion borders[4].

At every visit, all patients were monitored with Snellen visual acuity (VA), non-contact tonometry, biomicroscopy, dilated funduscopy and fundus drawing. Fundus photography was performed in some cases.

Intravitreal injections were performed in the special area of the outpatient eye clinic the same as a previously described technique[18]. In brief, the conjunctiva was cleaned with 5% povidone-iodine solution. Topical 0.4% oxybuprocaine was used as an anesthetic. The dose of ganciclovir used for intravitreal injections was 2 mg/0.1ml. Injections were performed with a 27-guage needle mounted on a tuberculin syringe through the pars plana, 4 mm from the limbus. A tobramycin eye drop was applied after injection.

Induction treatment consisted of weekly injections until the lesions were inactive. Maintenance therapy consisted of one injection each 2-4 weeks continuously until relapse, then the weekly schedule was re-started.

Visual outcome was analyzed in each eye separately by comparison of the visual acuity at baseline examination with the visual acuity at the time of the last follow up[4,18]. If visual acuity remained no change or changes of less than two lines of baseline on the Snellen chart, it was considered stable. Improvement or deterioration of two or more lines defined a significant change. Ocular complications of intravitreal injections were evaluated for each affected eye.

Statistical analysis and computations were performed with the statistical program, SPSS for Windows Version 10.0 (SPSS Inc., Chicago, USA). Frequency table with number and percentage were described with descriptive statistics (range, mean and SD)

The study protocol was approved by the research ethics committee of the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (No. 55/2003).

Results

Three hundred and sixty-three patients (568 eyes) were treated and followed for a mean period of 25.3 weeks (range, 18 to 118 weeks). Table 1 shows the

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

Characteristics	Number (%)
No. of patients	363
Age (yrs)	
Mean ± SD	34.5±7.6
Range	5-64
Sex	
Male	163 (45%)
Female	200 (55%)
Laterality at first	
Unilateral	203 (56%)
Bilateral	160 (44%)
Visual Acuity at initial visit (eyes) (N = 523 eyes)	
6/6-6/18	216 (41%)
< 6/18-3/60	142 (27%)
< 3/60 - PL	153 (29%)
No PL	12 (2%)
Location of lesions at initial visit (eyes)	
Zone 1	13 (2%)
Zone 2	168 (32%)
Zone 3	6 (1%)
Zone 1 and zone 2	229 (44%)
Zone 2 and zone 3	58 (11%)
Zone 1 and zone 2 and zone 3	49 (9%)

CMV = Cytomegalovirus

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

Results	Number (%)
No.of patients who developed CMV retinitis in the other eye	45 (22%)
Time of developed CMVR in the other eye (wks)	
Mean ± SD	9.5±10.0
Range	1-43
Visual outcome (eyes) (N = 568 eyes)	
Stable	343 (60%)
Improved	76 (13%)
Decreased	149 (26%)
Complications (eyes)	
Endophthalmitis	6
Retinal detachment	33
Vitreous hemorrhage	6
Cataract	2

CMV = Cytomegalovirus

baseline ocular characteristics of the patients at their first visit. The patients ranged in age from 5 to 64 years (mean 34.5 years). One hundred and sixty-three (45%) were male. Retinitis was initially unilateral in 203 patients (56%) and bilateral in 160 (44%). The visual acuity at initial presentation was in the 6/6 to 6/18 range in 216 eyes (41%), < 6/18-3/60 in 142 (27%), < 3/60-PL in 153 (29%), and no PL in 12 (2%). Retinitis affected only zone 1 in 13 eyes (2%), zone 2 in 168 (32%), zone 3 in 6 (1%), both zone 1 and zone 2 in 229 (44%), zone 2 and zone 3 in 58 (11%), and all three zones in 49 (9%) at the initial visit.

The results of intravitreal ganciclovir treatment are summarized in Table 2. Involvement of the fellow eye developed in 45 (22%) of 203 patients during treatment of the first eye, between 1 and 43 weeks (mean 9.5 weeks). In total, 568 eyes were injected with intravitreal ganciclovir. At the time of last follow up, 343 (60%) had stable vision, 76 (13%) had improved vision, and 149 (26%) had decreased vision. Complications in 568 treated eyes included 6 with endophthalmitis, 33 with retinal detachment, 6 with vitreous hemorrhages, and 2 with cataract.

Discussion

CMV retinitis is the most common sight-threatening complication in acquired immune deficiency syndrome (AIDS), occurring in 33 % of patients in Chiang Mai study[19]. Systemic treatment with ganciclovir has been the mainstay of management[1-8], but frequently was complicated by its toxicity and deterioration in quality of life[5,6,9,10]. Intravitreal ganciclovir has shown to be effective in stopping the progression of CMV retinitis in AIDS patients[11-16]. The authors therefore evaluated the efficacy of this drug in terms of the visual outcome, and complications of the treatment.

In the present study, eyes with stabilized, improved, and decreased visual outcome were 60%, 13%, and 26%, respectively (Table 2). If the eyes with initial visual acuity of no PL (12 eyes or 2%) were not taken into account for stabilized visual outcome, therefore 71% of eyes could preserve vision no worse than before by this treatment modality. Nevertheless, the initial visual acuity, location and extent of lesions, complications of diseases, and other AIDS-related disorders such as retinal ischemic associated with microvascular diseases and lesions involving intracranial visual pathways should also be considered to be the other factors that affected the visual outcome [4].

Bilateral disease occurred in 45 (22%) of 203 patients, who first came with unilateral involvement. It is known that intravitreal therapy is purely palliative as it has no effect on the systemic cytomegalovirus infection. However, systemic ganciclovir may not offer the expected advantage in this respect, since contralateral retinitis has been reported in 15-68% of patients receiving intravenous maintenance therapy[5-6,9-10]. In addition, frequent follow up meant that all second eye infections might be recognized early.

Six eyes had endophthalmitis, representing 1.1 % of 568 treated eyes. Multiple injections that required to maintain remission may be the risk factor that attributes to this serious complication of intravitreal injections. A previous author's study using intravitreal foscarnet reported an incidence of endophthalmitis of 1% of treated eyes[18]. Some studies advocated intra-

vitreal injections performed under sterile condition in the operating room would reduce this infection rate[11,12]. However, it may not be practical in a clinical setting treating large a number of patients.

There were 33 eyes (5.8%) with retinal detachments and 6 (1.2 %) with intravitreous hemorrhages. These rates are not different from those reported in other intravitreal series[11,12,14,16,18]. It was accepted that intravitreal injection was not attributed to these complication, since retinal detachment was a frequent complications of this disease, with an incidence varying from 11% to 29%[20,21]. Risk factor for development of rhegmatogenous retinal detachment in patients with CMV retinitis were peripheral involvement greater than 25%, the presence of active retinitis, greater patient age, and lower CD4+ cell counts[20,21]. It was also reported that intravitreal therapy offered a significant benefit over systemic therapy in the risk of CMV-related retinal detachment[22]. Although vitreous anomalies induced by ganciclovir (pH 10.14) was suspected to be a contributing factor[14], a previous author's study using foscarnet (pH 7.4) did not demonstrated this advantage[18].

Two patients developed cataract. None of them had evidence of trauma to the lens capsule that could be associated with intravitreal injections. Cataract was reported to be a rare complication of this technique[11-16].

Although there was a previous study using intravitreal foscarnet[18], the authors did not compare the result of both studies with statistical analysis. They were both not randomized controlled trials, and also shared the weakness inherent in all retrospective studies.

Considered as a whole, the present study showed clinical efficacy of intravitreal ganciclovir similar to other previously reported[11-16], but the complications of the intravitreal injections should also be recognized. Furthermore, concern for quality of life was one of the decisive factors, then the cost-effective analysis of treatment options for CMV retinitis in Thailand should be further studied.

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การรักษาจอประสาทตาอักเสบจากไซโตเมกะโลไวรัสในผู้ป่วยเอดส์ โดยการฉีดยาแกนไซโคล-เวียร์เข้าวุ้นตา

สมสงวน อัษญคุณ, ประภา ยูวะเวส, สุภพ งามทิพากร, จีระเดช ประสิทธิศิลป์

ความเป็นมา: *โรคจอประสาทตาอักเสบจากไซโตเมกะโลไวรัส เป็นโรคติดเชื้อฉวยโอกาสทางตาที่พบบ่อยที่สุดในผู้ป่วยกลุ่มอาการภูมิคุ้มกันบกพร่อง และมักทำให้ตาบอดได้ถ้าไม่ได้รับการรักษา การฉีดยาแกนไซโคลเวียร์เข้าวุ้นตาสามารถยับยั้งโรคได้*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพและผลแทรกซ้อนของการฉีดยาแกนไซโคลเวียร์เข้าวุ้นตา (2 มิลลิกรัม ใน 0.1 มิลลิลิตร) ในการยับยั้งโรคจอประสาทตาอักเสบจากไซโตเมกะโลไวรัส*

รูปแบบการวิจัย: *การศึกษาแบบย้อนหลังในกลุ่มผู้ป่วย*

วัสดุและวิธีการ: *ผู้ป่วยโรคจอประสาทตาอักเสบจากไซโตเมกะโลไวรัส 363 คน ที่มารักษาที่โรงพยาบาลมหาราชนครเชียงใหม่ ตั้งแต่มิถุนายน พ.ศ. 2544 ถึง ธันวาคม พ.ศ. 2546 โดยในระยะเริ่มต้นทำการฉีดยาสัปดาห์ละครั้งจนรอยโรคสงบ แล้วตามด้วยการฉีด 2-4 สัปดาห์ต่อครั้งไปตลอดจนรอยโรคลุกลามใหม่ก็จะเริ่มต้นฉีดยาสัปดาห์ละครั้งใหม่*

ผลการศึกษา: *ตาที่ได้รับการรักษา 568 ตา พบว่า มีสภาพการมองเห็นเมื่อสิ้นสุดการรักษา (ระยะเวลาเฉลี่ย 25.7 สัปดาห์) ดังนี้ สภาพการมองเห็นเท่าเดิม 343 ตา (60%) สภาพการมองเห็นดีขึ้น 76 ตา (13%) และสภาพการมองเห็นลดลง 149 ตา (26%) ภาวะแทรกซ้อนที่พบคือ จอภาพตาหลุด 33 ตา เลือดออกในน้ำวุ้นตา 6 ตา การอักเสบในลูกตา 6 ตา และต้อกระจก 2 ตา และผู้ป่วย 22% เกิดรอยโรคในตาอีกข้างหนึ่งในระหว่างการรักษาตาข้างแรก*

สรุป: *การรักษาด้วยการฉีดยาแกนไซโคลเวียร์เข้าวุ้นตาเป็นอีกทางเลือกหนึ่งในผู้ป่วยที่ไม่สามารถให้ยาต้านเชื้อไซโตเมกะโลไวรัสทางเส้นเลือดได้ แต่ผลแทรกซ้อนจากการฉีดยาเข้าวุ้นตาเป็นสิ่งที่ต้องคำนึงในการรักษาด้วย*