Treatment of Cytomegalovirus (CMV) Retinitis with Intravitreous Ganciclovir in HIV-Infected Children

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Objectives: To evaluate the efficacy, visual outcomes, and complications of intravitreous ganciclovir treatment in cytomegalovirus (CMV) retinitis in HIV-infected children.

Material and Method: The medical records of HIV-infected children who were screened for CMV retinitis from February 2002 to February 2005 were reviewed. The children with CD4+ <15%, or with clinical category C would have complete ophthalmic examination every 3 months. Ganciclovir (4 mg/0.04 ml) was administered intravitreously to the eye with CMV retinitis every 2 weeks under general anaesthesia. After injection, fundi were examined immediately, 1 day, 14 days and every 2 weeks until the lesions were stable.

Results: Six (9 eyes) out of 45 children (13%) aged 2-12 years were found to have CMV retinitis. All CMV retinitis lesions were "cheese and ketchup like" (retinal hemorrhage and exudate) lesions and presented in the posterior pole. Bilateral CMV retinitis were found in 3 children. Intravitreous ganciclovir was injected in 4 children (5 eyes). The average number of intravitreous injections for each patient was 5.6 (3-7) times. All of the children received antiretroviral therapy and 3 children also received intravenous ganciclovir. CMV retinitis lesions were improved in every eye. The visual acuity (VA) remained stable in 4 eyes, but endophthalmitis developed in one eye a few days after injection. The average duration of follow-up was 13.5 months (3-23 months).

Conclusion: CMV retinitis was not uncommon. The authors found that intravitreous ganciclovir was effective but may cause complications. This treatment should be considered in a resource-limited setting.

Keywords: CMV retinitis, Ganciclovir, AIDS

Cytomegalovirus (CMV) is an important cause of morbidity and mortality in immunocompromised individuals. Although CMV retinitis occurs in up to 40% of the adult AIDS population, it has been reported in approximately 6% of children with AIDS. Children with CMV retinitis may be unable to describe visual changes. There is usually no associated external ocular sign. These may lead to a delay in the diagnosis of CMV retinitis in HIV-infected pediatric population.

The optimal treatment of CMV retinitis in children has not been established. Current therapeutic regimens with ganciclovir and foscarnet are identical to those used in adults, with drug doses adjusted for body weight. Systemic treatment with ganciclovir or foscarnet have been the mainstay of management CMV retinitis and prevention of extraocular involvement, but frequently are complicated by relapse, toxicity, and deterioration in quality of life. Local therapy with implantation of a slow-release ganciclovir-containing reservoir is also recommended for the affected eyes. Intraocular ganciclovir implantation was superior to systemic ganciclovir for the affected eye in terms of longer time to relapse. Combination of systemic and local ganciclovir has been the preferred regimen. Because intraocular ganciclovir implantation is expensive and not available in a resource poor setting, intravitreous
Intravitreous injection is considered an alternative treatment. Intravitreous administration of ganciclovir is used primarily as salvage therapy for adult patients intolerant of systemic treatment and the relapsing rates have been similar to systemic treatment\(^{15-17}\).

In the present report, the authors described ocular features of CMV retinitis and assess efficacy, visual outcomes and complications of intravitreous ganciclovir injection for CMV retinitis in HIV-infected children.

**Material and Method**

The medical records of children who received ophthalmic examination during February 2002-2005 were reviewed. All patients met Centers for Disease Control (CDC) criteria for the diagnosis of AIDS\(^{18}\) stage “C” or “3” or these with ocular symptoms had ophthalmic examination routinely. The following data was obtained on initial examination: age, sex, staging of HIV according to CDC, CD4+ T-lymphocyte count, underlying systemic diseases, medications and fundus findings.

The clinical characteristic features of CMV retinitis included marked edema with dense, confluent areas of retinal whitening, accompanied by retinal hemorrhage and vascular sheathing or granular lesions.

The diagnosis criteria of CMV retinitis included the compatible clinical finding and positive CMV-PCR (CMV-polymerase chain reaction) of the vitreous specimen in all the cases in the present study. Because of intravitreous injection, the authors decided to perform vitreous tapping for CMV-PCR for only the present study.

For those with the disease, visual acuity, anterior segment, fundus, laterality of retinitis, and location of retinitis were recorded. Visual acuity assessment was based on the child’s age and cooperation; Snellen acuity, Allen picture, and visual fixation were performed. The location of CMV retinitis lesions were described as either within the posterior pole or in the peripheral retina. The posterior pole was defined as the retina enclosed by the major temporal vascular arcades or within 1 disc diameter (1,500 mm) from the nasal margin of the optic nerve. CMV retinitis lesion in the posterior pole was considered potentially sight threatening because of its proximity to the fovea and/or optic nerve\(^{13,19}\). The peripheral retina lesion extends anteriorly from the margin of the posterior pole to the ora serrata.

The children with CMV retinitis whose visual acuity more than hand motion were treated with intravitreous ganciclovir in the operating room except for those who were allergic to ganciclovir or derivatives. Those at risk under general anesthesia would be postponed. Bilateral injections were given as needed. The dose of intravitreous ganciclovir injection was 4 mg in 0.04 ml. Ganciclovir was divided and packed in sterile vial (40 mg/1 vial) under a sterile conditions by the hospital pharmacy. Each injection was given via 27-gauge needles through any quadrants of pars plana, 2-2.5 millimeters from the limbus in children 1-4 years of age and 3-3.5 millimeters in children over 4 years of age. Chloramphenicol eye ointment was applied immediately after intravitreous injection and followed by levofloxacin eye drop four times a day for 2 weeks. Intravitreous injections were performed every 2 weeks until CMV retinitis lesions were stable. Relapsing lesions were classified clinically by the presence of new lesions or extension of active retinitis by 750 micron from inactive borders and confirmed by fundus photography. Relapsing CMV retinitis was treated with once a week injections until resolution. Complications from intravitreous injection were recorded. After the first injection, fundi were examined immediately, 1 day, 14 days and every 2 weeks until CMV retinitis lesions were inactive. The data were summarized by case report with mean and range.

**Results**

There were 45 HIV-infected children who received ophthalmic examination. The ratio of males to females was 1.8:1. The mean age at first ophthalmic examination was 6.9 years (range 0.8 to 14 years). CMV retinitis was found in 6 children (9 eyes; 13%) (Table 1).

The average age at diagnosis of CMV retinitis was 7.1 years (range 2 to 12 years). Three patients (case 1, 2, and 3) had received antiretroviral therapy (ART) for 1-52 months when CMV retinitis was diagnosed. The CD4+ T-lymphocyte count at diagnosis of CMV retinitis ranged from 9 to 1500 cells/mm\(^3\) (0.24-16.39\%). Other concomitant diagnoses were pulmonary tuberculosis (TB), lymphoid interstitial pneumonitis (LIP), cardiomyopathy, hepatitis, chronic diarrhea and otitis media.

At initial examination, CMV retinitis lesions were presented bilateral in three (50%) of six children. Active retinitis involved the posterior pole in seven (83%) of nine eyes and occupied nearly total fundus in two eyes. Exudates and hemorrhages in fundus findings were found in all cases. One case (case 5) had a retinal hole adjacent to active CMV retinitis lesion. The authors treated the retinal hole with indirect laser retinopexy.
### Table 1. Clinical features of six children with CMV retinitis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age at diagnosis of CMV retinitis (yrs)</th>
<th>Staging of HIV</th>
<th>CD4⁺ count (cells/mm³) at diagnosis of CMV retinitis</th>
<th>CD4⁺ count (cells/mm³) at the initiation of ART</th>
<th>Medications</th>
<th>Duration of HAART at diagnosis of CMV retinitis (months)</th>
<th>Ocular symptom</th>
<th>Outcome</th>
<th>Other diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>7</td>
<td>C3</td>
<td>30 (1.10%)</td>
<td>394 (13.23%)</td>
<td>AZT, 3TC</td>
<td>4</td>
<td>NO</td>
<td>death</td>
<td>Pulm TB</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>9</td>
<td>C3</td>
<td>221 (6.46%)</td>
<td>394 (13.23%)</td>
<td>3TC, d4T, LPV/r, ganciclovir IV 2 weeks</td>
<td>0</td>
<td>Blurred vision</td>
<td>alive</td>
<td>Otitis media</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>6</td>
<td>C3</td>
<td>559 (16.39%)</td>
<td>559 (16.39%)</td>
<td>GPOvir</td>
<td>1</td>
<td>NO</td>
<td>alive</td>
<td>LIP</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>12</td>
<td>C3</td>
<td>9 (0.24%)</td>
<td>9 (0.24%)</td>
<td>AZT, 3TC, EFV, IRZE</td>
<td>0</td>
<td>Blurred vision</td>
<td>alive</td>
<td>Pulm TB, otitis media</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>2</td>
<td>C3</td>
<td>1500 (14%)</td>
<td>1500 (14%)</td>
<td>AZT, 3TC, NFV, ganciclovir IV 3 weeks</td>
<td>0</td>
<td>Blurred vision</td>
<td>stable</td>
<td>Pulm TB, cardiomyopathy, hepatitis</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>7</td>
<td>C3</td>
<td>28 (2.6%)</td>
<td>28 (2.6%)</td>
<td>GPOvir, ganciclovir IV 3 weeks</td>
<td>0</td>
<td>Blurred vision</td>
<td>alive</td>
<td>Pulm TB, chronic diarrhea</td>
</tr>
</tbody>
</table>

**ART** = anti-retroviral therapy; **CMV** = cytomegalovirus; **LIP** = lymphocytic interstitial pneumonitis; **Pulm TB** = pulmonary tuberculosis; **AZT** = zidovudine; **3TC** = lamivudine; **NFV** = Nelfinavir; **LPV/r** = lopinavir/ritonavir; **GPOvir** = d4T + 3TC + NVP (fixed-dose combination); **ddl** = didanosine; **d4T** = stavudine; **EFV** = efavirenz; ^ = received AZT + ddl for 29 months and then switched to 3TC + d4T + EFV for 18 months

### Table 2. Ophthalmologic features and treatment of six children with CMV retinitis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Laterality of CMV retinitis</th>
<th>Initial VA</th>
<th>Location of CMV retinitis</th>
<th>No. of ganciclovir intravitreous injections</th>
<th>Clinical response</th>
<th>Ocular outcome</th>
<th>Length of follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>LE</td>
<td>6/9, 6/6</td>
<td>LE : PP</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>LE</td>
<td>6/9, Hm</td>
<td>LE : PP</td>
<td>0</td>
<td>Phthisis</td>
<td>6/6, No Pl</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>RE</td>
<td>6/6, 6/6</td>
<td>RE : PP</td>
<td>3</td>
<td>Stable</td>
<td>6/6, 6/6</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>BE</td>
<td>Hm, 6/18</td>
<td>BE : PP</td>
<td>0**</td>
<td>Stable</td>
<td>No Pl, 1/60</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>BE</td>
<td>BE: F&amp;F</td>
<td>BE : PP</td>
<td>7</td>
<td>Stable</td>
<td>BE: F&amp;F</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>BE</td>
<td>Pl, 6/60</td>
<td>BE : nearly total retina</td>
<td>0**</td>
<td>Stable</td>
<td>No Pl, 6/10</td>
<td>4</td>
</tr>
</tbody>
</table>

**RE** = right eye; **LE** = left eye; **BE** = both eyes; **VA** = visual acuity; **Hm** = hand motion; **Pl** = light perception; **No Pl** = no light perception; **F&F** = fix and follow target; **PP** = posterior pole

* = the parent did not consent to get intravitreous injection

** = the eye without injection due to poor VA
In adults with AIDS, CMV retinitis is typically associated with a CD4+ T-lymphocyte count less than 50 cells/mm³ (23). CMV retinitis has been reported in pediatric patients with low CD4+ counts (20) (below 20 cells). In the present series, the CD4+ T-lymphocyte counts in five HIV-infected children were 30, 221, 9, 1500 and 28 cells/mm³, respectively, which were less than 15%. However, one child aged 6 years had CD4+ T-lymphocyte count 559 cells/mm³ (16.39%) at the time of diagnosis. This patient was on ART for 1 month before CMV retinitis was diagnosed. The authors hypothesized that after early period ART treatment, some patients' T-lymphocyte may increase in number but not in functions so the patients could have CMV retinitis despite high CD4+ counts.

CMV retinitis was bilateral in half of the children in the present series, higher than in adults that found bilateral involvement in approximately one third (24, 25). The fellow eye in unilateral case did not develop CMV retinitis in the present series. This was probably from highly active antiretroviral therapy (HAART).

In the present series, all cases were presented by retinal hemorrhage and exudates (cheese-ketchup type). Baumal CR et al (20) reported that 88% of CMV retinitis in immunosuppressed children involved the posterior pole. In the present patients, active lesions initially involved the posterior poles in 7 eyes and nearly total retina in 2 eyes. In adults with AIDS evaluated prospectively, CMV retinitis was confined to peripheral retina in approximately 50% of eyes at initial examination (27). The authors hypothesized that children may be unable to describe visual changes that may lead to a delay in diagnosis of CMV retinitis. There was no case of CMV-related retinal detachment in the present series, although it has occasionally been described in children and occurs in up to 30% of adult patients (6, 28-30).

In 1985 Pulido et al (31) first treated CMV retinitis with ganciclovir intravitreous injection. Many studies reported a favorable response to intermittent intravitreous therapy with ganciclovir in adults (15-17, 32-34). There is no study of intravitreous injection in HIV-infected children. In the present series, CMV retinitis lesions were stable in all eyes after treatment. Visual acuity was stable in 4 out of 5 eyes compared to before treatment. Sustained-release ganciclovir implantation was another option for local treatment but it has not been widely used because of high cost.

There was one episode of endophthalmitis in the present series, representing 3.6% of 28 injections.

Intravitreous ganciclovir was injected in 4 cases (case 3, 4, 5, 6 total 5 eyes). The left eye of case 2 and the right eye of case 4 and 6 did not receive intravitreous ganciclovir injection due to poor vision. The authors did not treat poor visual eyes because the authors thought that the patients would not gain any visual benefit. Number of intravitreous ganciclovir injections was 3 to 7 times (mean 5.6 times) per eye; with a total of 28 injections. Three cases (case 2, 5, and 6) received intravenous ganciclovir. CMV retinitis lesions were healed in every eye with intravitreous ganciclovir injection. Vision remained stable in 4 eyes; but one eye had endophthalmitis a few days after the 7th intravitreous injection. This episode responded well to intravitreous antibiotic injection (vancomycin 1 milligram and amikacin 0.25 milligrams). This case had to postpone the 3rd intravitreous ganciclovir injection longer than 2 weeks (4 weeks) after the second injection because his condition was not suitable for general anesthesia. This lead to relapse of CMV retinitis in that eye and drop of vision to 4/60. The final VA after endophthalmitis was 1/60. This was the only major complication out of 28 injections (3.6%) performed during the study period. Another minor complication was subconjunctival hemorrhage presented shortly after injection in one eye which resolved in 1-2 weeks.

One of the 2 children who did no receive intravitreous ganciclovir (case 1) died after 4 months follow up. This child did not receive ganciclovir intravitreous injection because his mother refused the therapy after discussion of risk and benefit of treatment. The other child (case 2) had poor vision (HM) of the affected eye. The other eye was not involved. She received intravenous ganciclovir to prevent this normal eye.

At the follow-up period with ranged from 3 to 23 months (mean, 13.5 months), 5 children were alive. Table 2 shows the ophthalmic features and treatment of CMV retinitis patients. One child (case 5) was 2 years of age and was unable to evaluate visual acuity changes.

Discussion
Cytomegalovirus (CMV) retinitis appears to be substantially lower in the HIV-infected pediatric patients than in the adult counterpart (4). The reported incidence of CMV retinitis was 3.4-11% in HIV infected pediatric patients (4, 6, 20-22) with a mean follow up time of 17.3-30 months period. In the present study 13% of children in stage “C3” developed CMV retinitis at the median age 7 years old.
The authors could not identify the organism. Other studies in adults reported in 0.2-0.6% (16,17,35) of injections. Subconjunctival hemorrhage was found in one eye. Other complications from intravitreous injection include retinal detachment and vitreous hemorrhage were not found in the present series.

In summary, CMV retinitis in HIV-infected children was less common than in adults. Most presentations were fulminant or hemorrhagic (“cheeseketchup”) lesions. Although low CD4+ T-lymphocyte count is typical, moderate CD4+ T-lymphocyte count may not exclude CMV retinitis. Intravitreous ganciclovir injection was an effective local treatment for CMV retinitis. Ophthalmic screening is the best method to diagnose CMV retinitis in young children because of the lack of visual symptoms. Early diagnosis and prompt treatment are important to preserve vision and prevent future visual morbidity.

References


การรักษาจอประสาทตาอักเสบจากเชื้อ CMVโดยการฉีดยา ganciclovir เข้าวูนตาในผู้ป่วยเด็กที่ติดเชื้อ HIV

ธรรมนูญ สุรชาติกำธรกุล, ถุลกับยา, โชคณัฐภูมิภูมิ, นิรันดร์ ธรรมนูญ, พิทยา HTMLเวช

วัตถุประสงค์: เพื่อประเมินประสิทธิภาพ, ระดับสายตาและผลแทรกซ้อนของการฉีดยา ganciclovir เข้าวูนตาในผู้ป่วยเด็กที่ติดเชื้อ HIV

วัสดุและวิธีการ: ศึกษาจากเวชระเบียนของผู้ป่วยเด็กที่ติดเชื้อ HIV ที่มี CD4<sub>+</sub> < 15% หรือมีลักษณะคลินิกระดับ C ที่ส่งมาตรวจทำการประสาทตาอักเสบจากเชื้อ CMV ตั้งแต่เดือนกุมภาพันธ์ พ.ศ. 2545 ถึงเดือนกันยายน พ.ศ. 2548 ผู้ป่วยเด็กจะได้รับการตรวจตาทุก 3 เดือน เมื่อพบผู้ป่วยที่มีจอประสาทตาอักเสบจาก CMV จะได้รับการฉีด ganciclovir 4 มิลลิกรัมใน 0.04 ซีซี เข้าวูนตาทุก 2 สัปดาห์ ภายใต้การดมยาสลบ หลังจากฉีดยาเข้าวูนตาผู้ป่วยจะได้รับการตรวจตาทุกเดือน ที่ 1 วัน, 14 วัน และทุก 2 สัปดาห์ จนกว่ารอยโรคจะลดลง

ผลการศึกษา: ผู้ป่วย 6 ราย (9 ตา) อายุ 2-12 ปี ที่มีผู้ป่วยเด็ก 45 ราย พบจอประสาทตาอักเสบ CMV คิดเป็น 13% ของผู้ป่วย ลักษณะรอยโรคของจอประสาทตาอักเสบเป็นชนิด cheese และ ketchup รอยโรคมีปรากฏผ่านบริเวณส่วนหลังของจอประสาทตา จอประสาทตาอักเสบพบ 2 ตาในผู้ป่วย 3 ราย ผู้ป่วย 4 ราย (5 ตา) ได้รับการฉีด ganciclovir เข้าวูนตาจำนวนเฉลี่ยของการฉีดในผู้ป่วยแต่ละรายคือ 5.6 ครั้ง (3-7 ครั้ง) มีผู้ป่วยเด็ก 3 รายได้ ganciclovir ทางหลอดดำด้วย และ 2 รายได้ ganciclovir ทางวูนตา รอยโรคจอประสาทตาอักเสบ CMV ดื้อทุกราย ระดับสายตาหลังจากฉีดยาเท่าเดิม 4 ตา แต่มี 1 ตาลดลงจากการเกิด endophthalmitis ระยะเวลาการติดตามผู้ป่วยเฉลี่ย 13.5 เดือน (3-23 เดือน)

สรุป: การรักษาจอประสาทตาอักเสบ CMV ด้วยการฉีด ganciclovir เข้าวูนตาสามารถทำให้รอยโรคสงบได้แต่ต้องระวังผลแทรกซ้อนจากการฉีดยา การรักษาวิธีนี้อาจมีความจำเป็นในประเทศที่กำลังพัฒนา